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(54) Title: 2'-5'-(5-CARBAMIMIDOYL-1H-HETEROARYL)-6-HYDROXYBIPHENYL-3-YL!- CARBOXYLIC ACID
DERIVATIVES AS FACTOR VIIA INHIBITORS

(57) Abstract: The present invention relates to novel inhibitors of Factors VIIa, IXa, Xa, XIa, in particular Factor VIIa, pharma-
ceutical compositions comprising these inhibitors, and methods for using these inhibitors for treating or preventing thromboembolic
disorders. Processes for preparing these inhibitors are also disclosed.

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2-5-(5-CARBAMIMIDOYL-1H-HETEROARYL)-6-HYDROXYBIPHENYL-3-YL-CARBOXYLIC ACID
DERIVATIVES AS FACTOR VIIA INHIBITORS

BACKGROUND OF THE INVENTION

This Application is based on and claims priority from U.S. Provisional Application No. 60/438,083 filed on January 08, 2003, which is incorporated herein by reference.

Field of invention

[001] The present invention relates to novel inhibitors of Factors VIIa, IXa, Xa, XIa, in particular Factor VIIa, pharmaceutical compositions comprising these inhibitors, and methods for using these inhibitors for treating or preventing thromboembolic disorders. Processes for preparing these inhibitors are also disclosed.

State of the Art

[002] Thrombosis results from a complex sequence of biochemical events, known as the coagulation cascade. A triggering event in coagulation is the binding of the serine protease Factor VIIa (FVIIa) found in the circulation, to tissue factor (TF), a receptor which is found on the surface of blood vessels after damage or inflammation. Once bound to TF, Factor VIIa catalyzes the formation of the serine protease Factor Xa, which subsequently forms the final protease in the cascade, thrombin.

[003] The clinical manifestations of thrombosis range from acute myocardial infarction (AMI or heart attack) and unstable angina (UA) which occur in the key blood vessels of the heart (coronary vasculature) to deep vein thrombosis (DVT) which is the formation of blood clots in lower extremities which often follows orthopedic surgery on the hip and knee, as well as general abdominal surgery and paralysis. Formation of DVT is a risk factor for the development of pulmonary embolism (PE) in which part of a blood clot formed in the lower extremities, breaks off and travels to the lung where it blocks the flow of blood. The unpredictable development of PE often leads to a fatal outcome. Thrombosis can also be generalized systemically, with microclot formation occurring throughout the vascular system. This condition, known as disseminated intravascular coagulation (DIC), can be a consequence of certain viral diseases such as Ebola, certain cancers and sepsis. Severe DIC can lead to a dramatic reduction in the coagulation factors due to the excessive activation of the clotting response which may result in multiple organ failure, hemorrhage and death.

[004] The formation or embolization of blood clots in the blood vessels of the brain is the key event resulting in ischemic stroke. Triggering factors that lead to stroke are atrial fibrillation or abnormal rhythm of the atria of the heart and atherosclerosis followed by thrombosis in the main artery leading from the heart to the brain (carotid artery). Over 600,000 individuals suffer strokes each year in the U.S. Two-thirds of these stroke victims suffer some disability, and one-third suffer permanent and severe disability. Accordingly, there is a need for antithrombotic agents for the treatment of a variety of thrombotic conditions. The present invention fulfills this and related needs.

SUMMARY OF THE INVENTION

[005] In one aspect this invention is directed to a compound selected from the group consisting of:

[006] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;

[007] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid;

[008] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;

[009] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;

[010] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;

[011] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;

[012] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;

[013] 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-nitro-4'-methyl-6-hydroxy-biphenyl-3-yl]acetic acid;

[014] 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]acetic acid;

[015] 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]acetic acid;

[016] 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-2',4'-difluoro-6-hydroxy-biphenyl-3-yl]acetic acid;

[017] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-nitro-6-hydroxy-biphenyl-3-yl]acetic acid;

- [018] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;
- [019] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;
- [020] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [021] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [022] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid;
- [023] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [024] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [025] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [026] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [027] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [028] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [029] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid;
- [030] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [031] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid;
- [032] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]propionic acid;
- [033] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid;
- [034] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid;

- [035] *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;
- [036] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;
- [037] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;
- [038] ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;
- [039] [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and
- [040] ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or
- [041] a pharmaceutically acceptable salt thereof.
- [042] Preferably:
- [043] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;
- [044] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid;
- [045] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;
- [046] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;
- [047] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;
- [048] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;
- [049] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;
- [050] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;
- [051] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;
- [052] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

- [053] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [054] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid;
- [055] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [056] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [057] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [058] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [059] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [060] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [061] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid;
- [062] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
- [063] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid;
- [064] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid;
- [065] *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;
- [066] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;
- [067] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;
- [068] ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;
- [069] [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and

- [070] ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or
- [071] a pharmaceutically acceptable salt thereof.
- [072] More preferably,
- [073] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;
- [074] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;
- [075] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6'-dihydroxy-biphenyl-3-yl]acetic acid;
- [076] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid;
- [077] *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;
- [078] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;
- [079] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;
- [080] ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;
- [081] [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and
- [082] ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or
- [083] a pharmaceutically acceptable salt thereof.
- [084] More preferably:
- [085] *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;
- [086] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;
- [087] 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;
- [088] ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;

[089] [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and

[090] ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or

[091] a pharmaceutically acceptable salt thereof.

[092] In a second aspect, this invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound selected from the group consisting of:

[093] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-nitro-4'-methyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-2',4'-difluoro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-nitro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminoethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-

benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid; ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate; [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or a pharmaceutically acceptable salt thereof. The pharmaceutical composition can contain a mixture of above compounds.

[094] In a third aspect, this invention is directed to a method of treating a disease in an animal mediated by Factors VIIa, IXa, Xa and/or XIa, preferably VIIa, which method comprises administering to said animal a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound selected from the group consisting of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-nitro-4'-methyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-2',4'-difluoro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-

carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-nitro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid; ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate; [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or a pharmaceutically acceptable salt thereof. The pharmaceutical composition can contain a mixture of above compounds.

[095] Preferably, the disorder is a thromboembolic disorder or cancer, more preferably a thromboembolic disorder. Preferably, the disorder is deep vein thrombosis.

[096] In a fourth aspect, this invention is directed to a method of treating a thromboembolic disorder in an animal which method comprises administering to said animal a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound selected from the group consisting of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-nitro-4'-methyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-2',4'-difluoro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-nitro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetaminomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-

biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid; ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate; [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or a pharmaceutically acceptable salt thereof in combination with another anticoagulant agent(s) independently selected from a group consisting of a thrombin inhibitor, factor IXa inhibitor, factor Xa inhibitor, Aspirin®, and Plavix®. Preferably, the disorder is deep vein thrombosis.

[097] In a fifth aspect, this invention is directed to a method for inhibiting the coagulation of a biological sample (e.g., stored blood products and samples) comprising the administration of a compound selected from the group consisting of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-nitro-4'-methyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-2',4'-difluoro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-nitro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methyaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-

biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminoethyl-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6'-dihydroxy-biphenyl-3-yl]acetic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminoethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid; ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate; [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or a pharmaceutically acceptable salt thereof.

[098] In a sixth aspect, this invention directed to the use of a compound selected from the group consisting of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 5-(5-carbamimidoyl-1*H*-

benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-nitro-4'-methyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-2',4'-difluoro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-nitro-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]propionic acid; 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid; 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid; 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid; ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate; [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-

acetate; or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in the treatment of a thromboembolic disorder or cancer in an animal. Preferably, the disorder is a thromboembolic disorder.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0099] The following terms, as used in the present specification and claims, are intended to have the meaning as defined below, unless indicated otherwise.

[0100] The present invention also includes the prodrugs of above compounds. The term prodrug is intended to represent covalently bonded carriers, which are capable of releasing the above compounds, when the prodrug is administered to a mammalian subject. Release of the active ingredient occurs *in vivo*. Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups however regenerate original functional groups by routine manipulation or *in vivo*. Prodrugs of above compounds include compounds wherein a hydroxy, amidino, ureido, or carboxylic group in the above compound is modified. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., *N,N*-dimethylaminocarbonyl) of hydroxy or acid functional groups in above compounds. Prodrugs of compounds of this invention are also within the scope of this invention.

[0101] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

[0102] acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

[0103] salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference.

[0104] A "pharmaceutically acceptable carrier or excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

[0105] "Treating" or "treatment" of a disease includes:

- (1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,
- (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or
- (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[0106] A "therapeutically effective amount" means the amount of above compounds that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

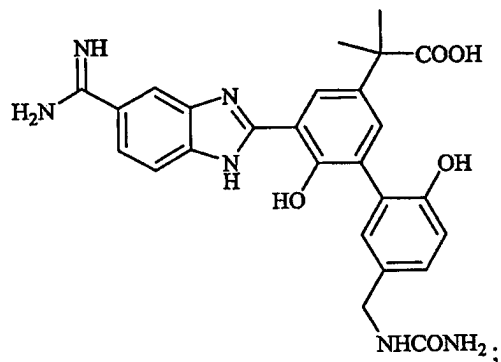
[0107] "Ureido" means a radical -NHCONH_2 .

[0108] The compounds of the present invention may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of materials. Many geometric isomers of olefins, C=C double bonds, and the like can be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, enantiomeric, diastereomeric, racemic forms and all geometric isomeric forms of a structure representing a compound of the

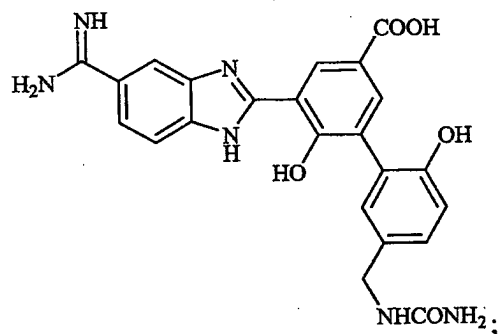
invention are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

[0109] Naming and structure: Structures and names of a representative number of compounds of the present invention are disclosed below.

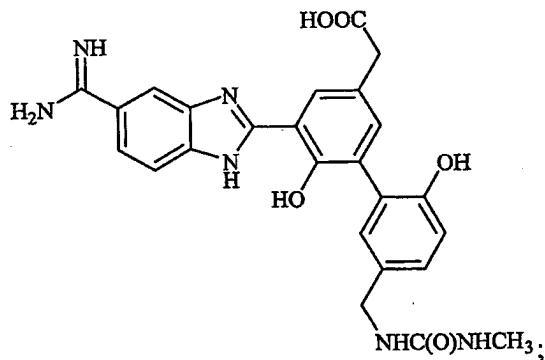
[0110] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid:



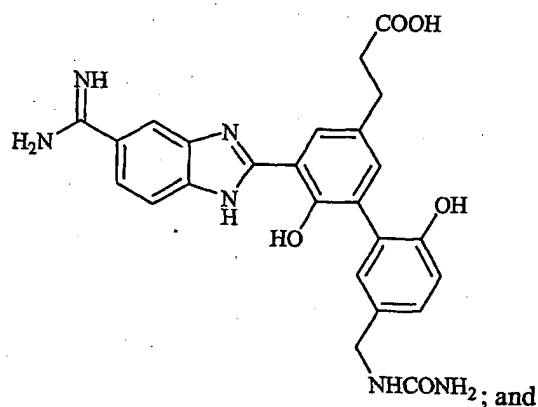
[0111] 5-[(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]carboxylic acid:



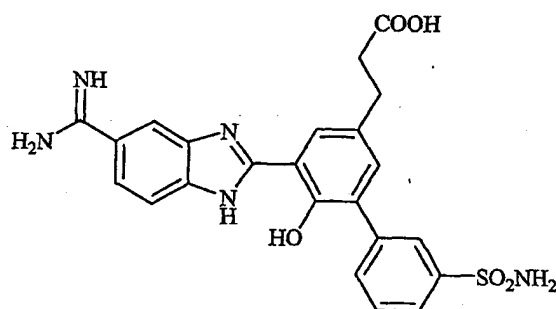
[0112] 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6'-dihydroxy-biphenyl-3-yl]acetic acid:



[0113] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid:



[0114] 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid:



Utility

[0115] The compounds of this invention inhibit Factors VIIa, IXa, Xa, and XIa, in particular Factor VIIa, and are therefore useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals.

[0116] Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis (e.g. DVT) and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis), and systemic embolism usually from the atrium during atrial fibrillation or from the left ventricle after transmural myocardial infarction, or caused by congestive heart failure; prophylaxis of reocclusion (i.e., thrombosis) after thrombolysis, percutaneous trans-luminal angioplasty (PTA) and coronary bypass operations; the prevention of rethrombosis after microsurgery and vascular surgery in general.

[0117] Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; anticoagulant treatment when blood is in contact with foreign surfaces

in the body such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device; and anticoagulant treatment when blood is in contact with medical devices outside the body such as during cardiovascular surgery using a heart-lung machine or in haemodialysis; the therapeutic and/or prophylactic treatment of idiopathic and adult respiratory distress syndrome, pulmonary fibrosis following treatment with radiation or chemotherapy, sepsis, septic shock, septicemia, inflammatory responses, which include, but are not limited to, edema, acute or chronic atherosclerosis such as coronary arterial disease and the formation of atherosclerotic plaques, cerebral arterial disease, cerebral infarction, cerebral thrombosis, cerebral embolism, peripheral arterial disease, ischaemia, angina (including unstable angina), reperfusion damage, restenosis after percutaneous trans-luminal angioplasty (PTA) and coronary artery bypass surgery.

[0118] The compounds of this invention can also be used in the treatment of cancer.

Testing

[0119] The ability of the compounds of this invention to inhibit factor VIIa and Xa can be tested *in vitro* and *in vivo* assays described in biological assays Example 1 and 2 below.

Administration and Pharmaceutical Compositions

[0120] In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. The actual amount of the compound of this invention, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

[0121] Therapeutically effective amounts of a compound of this invention may range from approximately 0.01-50 mg per kilogram body weight of the recipient per day; preferably about 0.1-20 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would most preferably be about 7 mg to 1.4 g per day.

[0122] In general, compounds of this invention will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral or parenteral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Oral compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained

release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

[0123] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[0124] The compositions are comprised of in general, a compound of the present invention in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of the present invention. Such excipient may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

[0125] Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

[0126] Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[0127] Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

[0128] The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of the present invention

based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt %. Representative pharmaceutical formulations containing a compound of this invention described below.

[0129] The compounds of this invention can be administered alone or in combination with other compounds of the present invention or in combination with one or more other active ingredient(s). For example, a compound of this invention can be administered in combination with another anticoagulant agent(s) independently selected from a group consisting of a thrombin inhibitor, a factor IXa, and a factor Xa inhibitor. Preferably, the thrombin inhibitor is Inogatran®, Melagatran® or prodrugs thereof which are disclosed in PCT Application Publication Nos. WO 94/29336 and WO 97/23499, the disclosures of which are incorporated herein by reference in their entirety. Factor Xa inhibitors that may be used in the combination products according to the invention include those described in *Current Opinion in Therapeutic Patents*, 1993, 1173-1179 and in international patent applications WO 00/20416, WO 00/12479, WO 00/09480, WO 00/08005, WO 99/64392, WO 99/62904, WO 99/57096, WO 99/52895, WO 99/50263, WO 99/50257, WO 99/50255, WO 99/50254, WO 99/48870, WO 99/47503, WO 99/42462, WO 99/42439, WO 99/40075, WO 99/37304, WO 99/36428, WO 99/33805, WO 99/33800, WO 99/32477, WO 99/32454, WO 99/31092, WID 99/26941, WO 99/26933, WO 99/26932, WO 99/26919, WO 99/26918, WO 99/25720, WO 99/16751, WO 99/16747, WO 99/12935, WO 99/12903, WO 99/11658, WO 99/11617, WO 99/10316, WO 99/07732, WO 99/07731, WO 99/05124, WO 99/00356, WO 99/00128, WO 99/00127, WO 99/00126, WO 99/00121, WO 98/57951, WO 98/57937, WO 98/57934, WO 98/54164, WO 98/46591, WO 98/31661, WO 98/28282, WO 98/28269, WO 98/25611, WO 98/24784, WO 98/22483, WO 98/16547, WO 98/16525, WO 98/16524, WO 98/16523, WO 98/15547, WO 98/11094, WO 98/07725, WO 98/06694, WO 98/01428, WO 97/48706, WO 97/46576, WO 97/46523, WO 97/38984, WO 97/30971, WO 97/30073, WO 97/29067, WO 97/24118, WO 97/23212, WO 97/21437, WO 97/08165, WO 97/05161, WO 96/40744, WO 96/40743, WO 96/40679, WO 96/40100, WO 96/38421, WO 96/28427, WO 96/19493, WO 96/16940, WO 95/28420, WO 94/13693, WO 00/24718, WO 99/55355, WO 99/51571, WO 99/40072, WO 99/26926, WO 98/51684, WO 97/48706, WO 97/24135, WO 97/11693, WO 00/01704, WO 00/71493, WO 00/71507, WO 00/71508, WO 00/71509, WO 00/71511, WO 00/71512, WO 00/71515, WO 00/71516, WO 00/13707, WO 00/31068, WO 00/32590, WO 00/33844, WO 00/35859, WO 00/35886, WO 00/38683, WO 00/39087, WO 00/39092, WO 00/39102, WO 00/39108, WO 00/39111, WO 00/39117, WO 00/39118, WO 00/39131, WO 00/40548, WO 00/40571, WO 00/40583, WO 00/40601, WO 00/47207, WO 00/47553, WO 00/47554, WO 00/47563, WO 00/47578, WO 00/51989, WO 00/53264, WO 00/59876,

WO 00/59902, WO 00/71510, WO 00/76970, WO 00/76971, WO 00/78747, WO 01/02356, WO 01/02397, WO 01/05784, WO 01/09093, WO 01/12600, WO 01/19788, WO 01/19795, WO 01/19798, WO 93/15756, WO 94/17817, WO 95/29189, WO 96/18644, WO 96/20689, WO 96/39380, WO 97/22712, WO 97/36580, WO 97/36865, WO 97/48687, WO 98/09987, WO 98/46626, WO 98/46627, WO 98/46628, WO 98/54132, WO 99/07730, WO 99/33458, WO 99/37643 and WO 99/64446; in US patents Nos. 6,034,093, 6,020,357, 5,994,375, 5,886,191, 5,849,519, 5,783,421, 5,731,315, 5,721,214, 5,693,641, 5,633,381, 5,612,378, 6,034,127, 5,670,479, 5,658,939, 5,658,930, 5,656,645, 5,656,600, 5,639,739, 5,741,819, 6,057,342, 6,060,491, 6,080,767, 6,087,487, 6,140,351, 6,395,731, and 5,646,165; in Japanese patent applications Nos. JP 99152269, JP 10017549, JP 10001467, JP 98017549, JP 00178243, JP 11140040, JP 12143623, JP 12204081, JP 12302765, JP 6327488 and JP 98001467; in European patent applications EP 937 723, EP 937 711, EP 874 629, EP 842 941, EP 728 758, EP 540 051, EP 419 099, EP 686 642, EP 1 016 663 and EP 529 715; and in German patent applications Nos. DE 19845153, DE 19835950, DE 19743435, DE 19829964, DE 19834751, DE 19839499, DE19900355, DE19900471 and DE 19530996, the specific and generic disclosures in all of which documents are hereby incorporated by reference.

[0130] Factor Xa inhibitors also include those disclosed in international patent applications WO 96/10022, WO 97/28129, WO 97/29104, WO 98/21188, WO 99/06371, WO 99/57099, WO 99/57112, WO 00/47573, WO 00/78749, WO 99/09027 and WO 99/57113, the specific and generic disclosures in all of which documents are hereby incorporated by reference, as well as 4-{4-[4-(5-chloroindol-2-ylsulfonyl) piperazine-1-carbonyl]phenyl}-pyridine-1-oxide and pharmaceutically acceptable derivatives thereof. Preferred Factor Xa inhibitors include antistatin, tick anticoagulant protein and those known as SQ-311 and SQ-315 (see international patent application WO 98/57951); SN-292 (see international patent application WO 98/28282); SN-429 and SN 116 (see international patent application WO 98/28269); RPR-208707 (see international patent application WO 98/25611 at Example 48); XU-817 (see international patent application WO 98/01428); SF-324 and SF-303 (see international patent application WO 97/23212); YM 60828 (see international patent application WO 96/16940 at Example 75); FACTOREX (see US patent No. 5,783,421); SF-324 (see European patent application EP 874 629); DX9065A (see European patent application EP 540 051 at Example 39); 1-(4-amidinobenzyl)-4-(6-chloronaphthalene-2-ylsulfonyl)-piperazin-2-one (see JP 12204081 at Example 2); M55555 (see international patent application WO 99/33805 at Example 39); DPC423 (1-(3-amidinophenyl)-2-(2'-aminolsulfonyl[1,1'-biphenyl]-4-ylaminocarbonyl)-4-bromopyrrole, see international patent

application WO 98/28269); 3-(3,5-difluoro-6-[3-(4,5-dihydro-1-methylimidazol-2-yl)-phenoxy]-4-[2,3-dihydroxy-propoxy]-pyridin-2-yloxy)-4-hydroxybenzamidine (see international patent application WO 00/31068); ZK-807834 (see international patent application WO 7/29067); 1,4-diaza-4-(6-chloro-naphthalene-2-ylsulfonyl)-6-(methoxymethyl)-7-oxa-1'-(pyridin-4-yl)spiro[bicyclo-[4-3.0]-nonane-8,4'-piperidine]-2-one (see international patent application WO 01/02397); (S)-1-(4-aminoquinazolin-7-ylmethyl)-4-[2-(5-chlorothien-2-yloxy)acetyl]-3-methoxy-methylpiperazin-2-one (see international patent application WO 00/32590); 3-(2-[4-(2-aminosulfonyl-phenyl)benzoylphenoxy]-benzamidine (see international patent application WO 01/19788); and 4-(2-[4-(5-chloroindol-2-yl-sulfonyl)-2-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl-carbonyl]-thiazol-5-yl)pyridine N-oxide (see Japanese patent application No. JP 12143623); as well as the compounds of Example 7 of international patent application WO 98/21188, of Examples 3 and 6 of WO 99/57113, of Example 6 of international patent application WO 00/78747, of Examples 188, 211 and 167 of US patent No. 6,080,767, of Examples 40, 54 and 55 of international patent application WO 99/33805, of Examples 5, 6, 8, 9, 10, 11, 12, 13, 15, 16 and 17 of international patent application WO 01/05784, of Examples 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 22, 23, 25, 26, 28, 29, 30, 31, 32, 33, 34, 38, 39, 40, 41, 42 and 43 of international patent application WO 01/12600, and of Examples 802 and 877 of international patent application WO 00/35886. Other anticoagulant agents that can be used in the combination therapy are those disclosed in U.S. Patent Applications Publication Nos. 20020065303, 20020061842, 20020058677, 20020058657, 20020055522, 20020055469, 20020052368, 20020040144, 20020035109, 20020032223, 20020028820, 20020025963, 20020019395, 20020019394, 20020016326, 20020013314, 20020002183, 20010046974, 20010044537, 20010044536, 20010025108, 20010023292, 20010023291, 20010021775, 20010020020033, 20010018423, 20010018414, and 20010000179, which are incorporated herein by reference in their entirety.

[0131] Suitable formulations for use in administering melagatran and derivatives (including prodrugs) thereof are described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 99/27912, WO 99/27913, WO 00/12043 and WO 00/13671, the disclosures in which documents are hereby incorporated by reference.

[0132] Similarly, suitable formulations for use in administering Factor Xa inhibitors and derivatives (including prodrugs) thereof are described in the literature, for example as described in the prior art documents relating to Factor Xa inhibitors that are mentioned hereinbefore, the disclosures in which documents are hereby incorporated by reference.

Otherwise, the preparation of suitable formulations, and in particular combined preparations including both melagatran/derivative and Factor Xa inhibitor/derivative may be achieved non-inventively by the skilled person using routine techniques. The amounts of melagatran, Factor Xa inhibitor, or derivative of either, in the respective formulation(s) will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

[0133] Suitable doses of melagatran, Factor Xa inhibitors and derivatives of either, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the prior art documents relating to melagatran (or derivatives (including prodrugs) thereof), and to Factor Xa inhibitors, that are mentioned hereinbefore, the disclosures in which documents are hereby incorporated by reference.

EXAMPLES

[0134] The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Synthetic Examples

[0135] REFERENCE 1

Synthesis of 2-[3-bromo-4-(2-methoxyethoxymethoxy)-phenyl]-N-(2-methoxyethoxymethyl)acetamide

Step 1

[0136] Methyl 4-hydroxyphenyl acetate (10.5 g, 63 mmol) was dissolved in acetic acid (200 mL) and then a solution of bromine (3.6 mL, 69.5 mmol in acetic acid) was added over 1 hour. The mixture was stirred overnight and then concentrated. Purification of product from the residue by column chromatography gave methyl 3-bromo-4-hydroxy-phenylacetate.

[0137] Methyl 3-bromo-4-hydroxy-phenylacetate was dissolved in methanol (20 mL) and the solution was charged with 28% ammonium hydroxide (10 mL). The mixture was stirred at room temperature for 3 days and concentrated. The remaining mixture was acidified with 4N hydrochloric acid and then extracted with ethyl acetate. The organic phase was dried and concentrated to give 3-bromo-4-hydroxy-phenylacetamide as a white solid. LCMS: Calcd: 230; Obsd (M⁺): 230.

Step 2

[0138] 3-Bromo-4-hydroxy-phenylacetamide (1.53 g, 6.91 mmol, 1.0 eq.) was dissolved in dichloromethane (30 mL) and the solution charged with 1-chloromethoxy-2-methoxyethane (3.22 g, 25.84 mmol, 2.3 eq.) and *N,N*-diisopropylethylamine (2.83 g, 21.87 mmol, 3.17 eq.) over 2 hours at room temperature. The mixture was washed with 5% citric acid and extracted with dichloromethane (x 2). The organic phase was dried and concentrated to give 2-[3-bromo-4-(2-methoxy-ethoxymethoxy)-phenyl]-*N*-(2-methoxy-ethoxymethyl)-acetamide. LCMS: Calcd: 406; Obsd (M⁺): 406.

[0139] REFERENCE 2

Synthesis of *tert*-butyl (3-bromobenzyl)-carbamate

[0140] Sodium hydroxide (8.76 g, 219.0 mmol, 2.2 eq.), di-*tert*-butyl dicarbonate (26.07 g, 119.45 mmol, 1.2 eq.) and water (100 mL) were added to a stirring solution of 3-bromobenzylamine (22.11 g, 99.55 mmol, 1.0 eq.) in tetrahydrofuran (75 mL) over 30 minutes at room temperature. The mixture was extracted with dichloromethane and water twice. The organic phase was dried and concentrated to give *tert*-butyl (3-bromobenzyl)-carbamate (34.88g, 100%). LCMS: Calcd 286; Obsd (M+23) 309).

[0141] REFERENCE 3

Synthesis of methyl 4-benzyloxy-3-bromo-5-formylbenzoate

[0142] Benzyl bromide (8.35 g, 48.83 mmol) and K₂CO₃ (6.74 g, 48.83 mmol) were added to a solution of methyl 3-bromo-5-formyl-4-hydroxy-benzoate (11.5 g, 44.39 mmol) in acetone (100 mL) and the mixture was stirred overnight. The organic layer was separated and washed with water, dried (MgSO₄) and concentrated. Product was purified from the residue by flash silica gel chromatography to give methyl 4-benzyloxy-3-bromo-5-formylbenzoate (10.0 g, 65%). ¹H NMR (400 MHz, DMSO-d₆) δ 10.00 (s, 1H), 8.41 (d, *J*=2.71, 1H), 8.21 (d, *J*=2.51, 1H), 7.46 (m, 2H), 7.38 (m, 3H), 5.22 (s, 2H), 3.88 (s, 3H). ESIMS m/z: M⁺ 370.9, 372.9.

[0143] REFERENCE 4

Synthesis of 3-bromo-4-methoxyphenylsulfonamide

Step 1

[0144] *o*-Bromoanisole (1.87 g, 10.0 mmol) was dissolved in chloroform (5 mL) and the solution was cooled in an ice-salt bath to -5° C to 0° C. The solution was carefully charged with chlorosulfonic acid (2.0 mL, 30.0 mmol) over 30 minutes and then allowed to warm to room temperature over 1 hour. The mixture was poured onto chopped ice and transferred to separatory funnel. The organic layer was separated and the aqueous layer was extracted, dried and concentrated to give 3-bromo-4-methoxyphenylsulfonyl chloride (2.80 g, 98%).

Step 2

[0145] 3-Bromo-4-methoxyphenylsulfonyl chloride (2.80 g, 9.8 mmol) was dissolved in dichloromethane (200 mL) and the solution treated with a solution of 0.5 M ammonia in dioxane (100 mL) and triethylamine (5 mL) for 2 hours. The reaction mixture was poured onto a mixture consisting of a 5% citric acid solution and dichloromethane. The organic layer was separated and the aqueous layer was extracted dichloromethane. The extracts were dried and concentrated to give 3-bromo-4-methoxyphenylsulfonamide (2.65 g, 100%).

[0146] REFERENCE 5

Synthesis of 2-bromo-1-(2-methoxyethoxymethoxy)-4-[2-(2-methoxyethoxymethoxy)ethyl]benzene

Step 1

[0147] Bromine (0.716 mL, 13.9 mmol) in acetic acid (30 mL) was added to a stirred solution of 4-hydroxyphenethyl alcohol (1.74 g, 12.6 mmol) in acetic acid (40 mL) over 30 minutes. The mixture was stirred overnight and then concentrated. The residue was dissolved in methanol (100 mL) and sufficient 2 M potassium carbonate solution was added to bring the pH to ~11. The mixture was stirred overnight and then acidified with hydrochloric acid, extracted with dichloromethane (DCM) and concentrated to give 2-bromo-4-(2-hydroxyethyl)-phenol.

Step 2

[0148] 2-Bromo-4-(2-hydroxyethyl)phenol (2.76 g, 12.6 mmol) was dissolved in DCM (300 mL) and the solution was treated with diisopropylethylamine (6.58 mL, 38 mmol) and 1-chloromethoxy-2-methoxyethane (4.34 mL, 38 mmol). The mixture was stirred overnight and then the DCM layer was separated, washed several times with 5% citric acid solution, dried and concentrated. Purification of product from the residue with 30 g of silica gel (30% ethyl acetate/hexane) gave 2-bromo-1-(2-methoxyethoxymethoxy)-4-[2-(2-methoxyethoxymethoxy)ethyl]benzene (4.95 g, 100%).

[0149] REFERENCE 6

Synthesis of 1-[3-Bromo-4-(2-methoxyethoxymethoxy)benzyl]-3-methylurea

Step 1

[0150] Diisopropyl-ethylamine (21.8 mL, 151.5 mmol) was added slowly to a magnetically stirred solution of 3-bromo-4-hydroxybenzonitrile (10 g, 50.5 mmol) and methoxyethoxymethylchloride (6.9 mL, 60.6 mmol) in dichloromethane (100 mL) and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was washed with 5% citric acid solution until the washings were acidic, then dried and concentrated. Chromatography of the resulting residue (silica gel, 30% ethyl acetate/hexanes) gave 3-bromo-4-(2-methoxyethoxymethoxy)-benzonitrile (11.5 g).

Step 2

[0151] Borane-tetrahydrofuran complex (1 M, 280 mL, 280 mmol) was added to a magnetically stirred solution of 3-bromo-4-(2-methoxyethoxymethoxy)-benzonitrile (10 g, 35 mmol) in THF (20 mL) and the reaction mixture was refluxed for 30 minutes. The reaction mixture was cooled to 0 °C and 1 N hydrochloric acid was added very slowly until the pH was acidic. THF from the reaction mixture was evaporated off and the remaining aqueous layer was washed with ethyl ether. The aqueous extract was basified with 2 N sodium hydroxide (until alkaline pH) and then extracted with ethyl acetate. The organic layer was washed brine and dried over anhydrous sodium sulfate. Evaporation of the volatiles gave 3-bromo-4-(2-methoxy-ethoxymethoxy)benzylamine (5.6 g) which was utilized in the next step without further purification.

Step 3

[0152] Methyl isocyanate (0.43 mL, 7.2 mmol) and triethylamine (1.0 mL, 7.2 mmol) was added to a solution of 3-bromo-4-(2-methoxyethoxymethoxy)-benzylamine (1.05 g, 3.60 mmol) in DMF (15 mL) and the mixture was stirred for 30 minutes. The mixture was concentrated and the residue was dissolved in ethyl acetate. The solution was washed several times with 5% citric acid and concentrated. Purification of product from the residue by silica gel chromatography (50% ethyl acetate/hexane, ethyl acetate, 10% methanol/ethyl acetate) gave 1-[3-bromo-4-(2-methoxyethoxymethoxy)benzyl]-3-methylurea (1.13 g, 90%).

[0153] REFERENCE 7**Synthesis of 3-bromo-4-(2-methoxyethoxymethoxy)acetophenone****Step 1**

[0154] 2-Bromophenol (1.16 mL, 10.0 mmol) was dissolved in carbon disulfide (10 mL) that had been cooled in an ice-salt bath under stirring. Anhydrous aluminum chloride (2.7 g, 20.0 mmol) was added in portions and then acetyl chloride (0.754 mL, 11.0 mmol) was added to the mixture. The mixture was stirred for one hour, refluxed overnight and then a mixture of 1M hydrochloric acid and ice was added. The mixture was extracted with DCM (x3) and the combined extracts were dried and concentrated. Chromatographed of the residue over 30 g of silica gel (20% ethyl acetate/hexane, 40% ethyl acetate/hexane) gave 3-bromo-4-hydroxyacetophenone (2.28 g, 53%).

Step 2

[0155] 3-Bromo-4-hydroxyacetophenone (2.15 g, 10.0 mmol) was dissolved in DCM and the solution was charged with diisopropylethylamine (2.61 mL, 15 mmol) and 1-chloromethoxy-2-methoxy-ethane (1.71 mL, 15.0 mmol). The mixture was stirred overnight and concentrated. The residue was dissolved in ethyl acetate and the solution was washed with 5% citric acid solution, dried and concentrated to give 3-bromo-4-(2-methoxyethoxymethoxy)-acetophenone (3.0 g, 100%).

[0156] REFERENCE 8**Synthesis of *N*-3-bromo-4-(2-methoxyethoxymethoxy)benzylacetamide**

[0157] 3-Bromo-4-(2-methoxyethoxymethoxy)benzylamine (0.58 g, 2.0 mmol) was dissolved in DCM (25 mL) and acetic anhydride (0.28 mL, 3.0 mmol) was added with triethylamine (0.42 mL, 3.0 mmol) to the solution. The mixture was stirred overnight and then poured onto a DCM/5% citric acid solution. The aqueous layer was extracted several more times and the combined organic layer was dried and concentrated to give *N*-3-bromo-4-(2-methoxyethoxymethoxy)benzylacetamide.

[0158] REFERENCE 9**Synthesis of methyl 5-bromo-3-formyl-4-(2-methoxyethoxymethoxy)-phenylacetate****Step 1**

[0159] Commercially available 4-methoxyphenylacetic acid (16.6g, 0.1 mol) was dissolved in acetic acid (120 mL) and stirred vigorously at approximately 0 °C. A solution of elemental bromine (16.0 g, 0.1 mol) in acetic acid (40 mL) was added dropwise over 45 minutes,

ensuring that the mixture did not freeze. The reaction mixture was allowed to warm slowly to room temperature and stir overnight. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was collected, washed with water, brine and 5% aqueous NaHSO₃, filtered and concentrated in vacuo to give 3-bromo-4-methoxyphenylacetic acid (24.24 g, 98%) as a yellow powder.

Step 2

[0160] A 250 mL round bottom flask was charged with 3-bromo-4-methoxyphenylacetic acid (14.0 g, 0.057 mol) and dry dichloromethane (100 mL). Nitrogen gas was bubbled through the reaction mixture for five minutes and then boron tribromide (1M in dichloromethane, 63 mL, 0.063 mol) was added very slowly via an addition funnel. The reaction was allowed to continue at room temperature for 2 hours while a white crystals gradually formed in the flask. The crystals were collected by filtration and washed repeatedly with dichloromethane to give 3-bromo-4-hydroxyphenylacetic acid (12 g, 92%).

Step 3

[0161] A solution of 3-bromo-4-hydroxyphenylacetic acid (12.0 g, 0.052 mol) in methanol was stirred at room temperature and ten drops of thionyl chloride were added. The reaction was allowed to continue for 2 hours and then the solvent was removed under reduced pressure. The residue was taken up in saturated aqueous sodium bicarbonate and the solution was extracted with diethyl ether (x3). The organic layers were collected, washed with water and brine, dried over MgSO₄ and concentrated in vacuo to give methyl-3-bromo-4-hydroxyphenylacetate as a golden oil (12.6 g, 99%).

Step 4

[0162] Proceeding as in Reference 10, Step 3, but substituting methyl-3-bromo-4-hydroxyphenylacetate gave methyl-3-formyl-4-hydroxy-5-bromophenylacetate.

Step 5

[0163] Diisopropyl ethylamine (11.3 mL, 60 mmols) was added slowly to a magnetically stirred solution of 5-bromo-3-formyl-4-hydroxy-phenylacetate (11 gm, 40 mmols) and 1-chloromethoxy-2-methoxy-ethane (6.9 mL, 60 mmols) in dichloromethane (100 mL) and the mixture was stirred at room temperature for 30 minutes. The dichloromethane solution was washed with 5% citric acid solution until the washings were acidic, then dried and concentrated. Chromatography of the resulting residue (silica gel, 30% ethyl acetate/hexane) gave 5-bromo-3-formyl-4-(2-methoxyethoxymethoxy)-phenylacetate (11.5 gm). MS LCMS Q⁺ 384 (M+23).

[0164] Proceeding as in Reference 9 above, but substituting 3-[5-bromo-3-formyl-4-hydroxyphenyl]propionic acid methyl ester (5 gm, 17 mmol), 1-chloromethoxy-2-methoxy-

ethane (4.7 mL, 17 mmol)) and diisopropyl amine (3.2 mL, 17 mmol) gave 3-[5-bromo-3-formyl-4-(2-methoxyethoxymethoxy)phenyl]propionic acid methyl ester (5.4 gm). MS LCMS Q⁺ 393 (M+23).

[0165] REFERENCE 10

Synthesis of 2-(3-bromo-5-formyl-4-hydroxyphenyl)-2-methyl-propionic acid methyl ester

Step 1

[0166] A solution of methyl 2-[4-(2-methoxy-ethoxymethoxy)-phenyl]-acetate (5.1 g, 20 mmol) was added dropwise to a suspension of sodium hydride (1.44 g, 60 mmol) in DMF (50 mL). The mixture was stirred for 30 minutes and then cooled to 10 °C. Methyl iodide (7.6 g, 50 mmol) was added in small portions and the mixture was stirred for 14 hours, quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and then brine, dried (magnesium sulfate) and concentrated in vacuum to give methyl 2-[4-(2-methoxy-ethoxymethoxy)-phenyl]-2-methyl-propionate (5.5 g, 97%).

Step 2

[0167] Methyl 2-[4-(2-methoxyethoxymethoxy)-phenyl]-2-methyl-propionate (5.5 g, 19.2 mmol) was dissolved in methanol (25 mL) and a 4N solution of hydrogen chloride in dioxane (25 mL) were added to the solution. The mixture was stirred for 4 hours and then the solvents were removed in vacuum. The residue was partitioned between water and ethyl acetate and the organic layer was separated and washed with water and then brine and dried over magnesium sulfate. The solvent was then removed in vacuum to provide methyl 2-(4-hydroxy-phenyl)-2-methyl-propionate (3.35 g, 90%).

Step 3

[0168] Magnesium chloride (1.1 g, 21 mmol) was added in one portion to a stirring mixture of methyl 2-(4-hydroxy-phenyl)-2-methyl-propionate (2.7 g, 14 mmol), paraformaldehyde (3.0 g, 98 mmol) and triethylamine (5.6 g, 56 mmol) in acetonitrile (125 mL). The mixture was heated under reflux for 3 hours, cooled and then poured into cold 1N aqueous hydrochloric acid. The product was extracted with ethyl acetate and the extract was washed with water and then brine and dried over magnesium sulfate. The solvent was removed in vacuum to give methyl 2-(3-formyl-4-hydroxy-phenyl)-2-methyl-propionate (2.6g, 84%).

Step 4

[0169] A solution of *N*-bromosuccinimide (2.3 g, 12.9 mmol) in DMF (15 mL) was added dropwise to a solution of methyl 2-(3-formyl-4-hydroxy-phenyl)-2-methyl-propionate (2.6 g,

11.7 mmol) in DMF (25 mL). The mixture was stirred for 3 hours and then partitioned between water and ethyl acetate. The organic layer was separated and washed with water and then brine and dried over magnesium sulfate. The solvent was removed to give methyl 2-(3-bromo-5-formyl-4-hydroxy-phenyl)-2-methyl-propionate (3.1 g, 88%).

[0170] Proceeding as in Reference 10, Steps 2-4), but substituting methyl 3-[4-(2-methoxyethoxymethoxy)-phenyl]-propionate gave methyl 3-(3-bromo-5-formyl-4-hydroxy-phenyl)-propionate.

[0171] REFERENCE 11

Synthesis of 5-aminocarbonyl-2-(2-methoxyethoxymethoxy)-bromobenzene

[0172] 3-Bromo-4-(2-methoxyethoxymethoxy)benzonitrile (1.28 gm, 4.5 mmol), prepared as in Reference 13, Step 1, was dissolved in methanol (10 mL) and the solution was treated with NaBO_3 (18mmol) in water (5 mL). The reaction mixture heated at 50 °C for 7 hours. The product was extracted with ethyl acetate to afford 4-aminocarbonyl-2-(methoxyethoxymethoxy)-bromobenzene (1.32 g).

[0173] REFERENCE 12

Synthesis of *N-tert*-butyl-3-bromobenzenesulfonamide

[0174] *tert*-Butylamine (3.14 g, 3.0 mmol, 1.1 eq.) and triethylamine (5.94 g, 58.6 mmol, 1.5 eq.) were dissolved in dichloromethane (20 mL) and the solution was stirred at room temperature while 3-bromobenzenesulfonyl chloride (10.0 g, 39.1 mmol) was added slowly. The mixture was stirred for 1 hour and then concentrated by evaporation under reduced pressure. The residue is taken up in 5% citric acid and ethyl acetate. The organic layer was washed repeatedly with brine and water and dried over anhydrous magnesium sulfate. Evaporation of the filtrate gave *N-tert*-butyl-3-bromobenzenesulfonamide as a white powder (10.94 g).

[0175] REFERENCE 13

Synthesis of 4-(2-methoxy-ethoxymethoxy)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile

Step 1

[0176] Methoxyethoxymethyl chloride (7.87 g, 7.21 mL, 63.2 mmol) and *N,N*-diisopropylethylamine (8.84 g, 11.9 mL, 68.4 mmol) were added to a solution of 3-bromo-4-hydroxy-benzonitrile (10.0 g, 52.6 mmol) in dichloromethane (250 mL). The mixture was stirred 2 hours and the organic layer was washed with water, dried (MgSO₄) and concentrated to give 3-bromo-4-(2-methoxy-ethoxymethoxy)-benzonitrile. HPLC (C-18 reverse phase) 3.734 min (1-90S).

Step 2

[0177] 3-Bromo-4-(2-methoxy-ethoxymethoxy)-benzonitrile (5.20 g, 18.2 mmol), dioxane (180 mL), bis(pinacolato)diboron (5.54 g, 21.8 mmol) and potassium acetate (5.35 g, 54.5 mmol) were combined in a 250 mL 24/40 round bottom flask. Argon was bubbled through the mixture and then dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II)dichloromethane adduct (purchased from STREM cat# 46-0450) (0.74 g, 0.91 mmol) was added and the solution was refluxed for 4 hours. The solution was allowed to cool and then was taken up in ethyl acetate (100 mL), washed with 5% citric acid and then brine and dried. The solvent was removed under reduced pressure and the residue was taken up in toluene (180 mL) to generate a 0.1 M solution of 4-(2-methoxy-ethoxymethoxy)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile.

[0178] Proceeding as in Reference 13 above, but substituting:

[0179] 3-bromo-*N-tert*-butyl-benzenesulfonamide gave *N-tert*-butyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide;

[0180] methyl [5-bromo-[3-formyl-4-(2-methoxy-ethoxymethoxy)-phenyl]]-acetate gave methyl [3-formyl-4-(2-methoxy-ethoxymethoxy)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]acetate;

[0181] methyl [5-bromo-4-(2-methoxyethoxymethoxy)phenyl]acetate gave methyl 2-[4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)phenyl]acetate;

[0182] 1-bromo-5-fluoro-2-methoxy-phenyl gave 2-(5-fluoro-2-methoxy-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane;

[0183] methyl [5-bromo-3-formyl-4-hydroxy-phenyl]-acetate gave methyl [3-formyl-4-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]acetate;

[0184] methyl 3-[5-bromo-3-formyl-4-hydroxy-phenyl]-propionate gave methyl 3-[3-formyl-4-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-propionate; and

[0185] methyl 3-[5-bromo-3-formyl-4-(2-methoxy-ethoxymethoxy)-phenyl]-propionate gave methyl 3-[3-formyl-4-(2-methoxy-ethoxymethoxy)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-propionate.

[0186] REFERENCE 14

Synthesis of methyl 2-(5-formyl-6,2'-bis-(2-methoxy-ethoxymethoxy)-5'-{[(2-methoxy-ethoxymethyl)-carbamoyl]-methyl}-biphenyl-3-yl)-acetate

[0187] 2-[3-Bromo-4-(2-methoxy-ethoxymethoxy)-phenyl]-N-(2-methoxy-ethoxymethyl)-acetamide (1.87g, 4.61 mmol, 1.2 eq.) was dissolved in a 0.1 M solution of methyl 3-formyl-4-(2-methoxyethoxymethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl acetate in toluene (3.84 mmol, 38.4 mL, 1.0 eq.). This solution was charged with 2.88 mL of 1 M potassium carbonate and nitrogen was bubbled in for five minutes. Tetrakis palladium (1.11 g, 0.98 mmol, 0.25 eq.) was added and the mixture was refluxed for 3 to 4 hours. The reaction mixture was poured onto ethyl acetate and the mixture was washed several times with 5% citric acid solution, dried and concentration by evaporation. The residue was subjected to 100 g of silica gel (30% ethyl acetate/hexane to 50% ethyl acetate/hexane) to give methyl 2-(5-formyl-6,2'-bis-(2-methoxy-ethoxymethoxy)-5'-{[(2-methoxy-ethoxymethyl)-carbamoyl]-methyl}-biphenyl-3-yl)-acetate. LCMS: Calcd 607; Obsd (M+23+1) 631.

[0188] Proceeding as in the Reference 14, but substituting *tert*-butyl (3-bromo-benzyl)-carbamate (2.1g, 7.35 mmol, 1.2 eq.) and methyl 3-formyl-4-(2-methoxyethoxymethyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenylacetate in toluene (612 mmol, 61.2 mL, 1.0 eq.), gave methyl 2-[3'-(*tert*-butoxycarbonylamino-methyl)-5-formyl-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate (2.65 g, 85%). LCMS: Calcd 487; Obsd (M+23) 510.

[0189] Proceeding as in Reference 14, but substituting methyl [5-bromo-3-formyl-4-(2-methoxy-ethoxymethoxy)-phenyl]acetate (1.0 g, 2.77 mmol) and *N-tert*-butyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide (890 mg, 3.06 mmol) gave methyl 2-[3'-*tert*-butylsulfamoyl-5-formyl-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate (1.88 g, 80%).

[0190] Proceeding as in Reference 14, but substituting methyl [3-formyl-4-(2-methoxy-ethoxymethoxy)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]acetate (2.54 g,

6.25 mmol) and 3-bromo-*N*-methyl-benzenesulfonamide (1.30 g, 5.2 mmol), gave methyl 2-[5-formyl-6-(2-methoxy-ethoxymethoxy)-3'-methylsulfamoyl-biphenyl-3-yl]-acetate (820 mg, 60%).

[0191] Proceeding as in Reference 14, but substituting methyl 2-(3-bromo-5-formyl-4-hydroxy-phenyl)-2-methyl-propionate (301 mg, 1.0 mmol) and *N*-*tert*-butyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide (373 mg, 1.1 mmol), gave methyl 2-(3'-*tert*-butylsulfamoyl-5-formyl-6-hydroxy-biphenyl-3-yl)-2-methyl-propionate (280 mg, 65%).

[0192] Proceeding as in Reference 14, but substituting methyl 3-(3-bromo-5-formyl-4-hydroxy-phenyl)-propionate (525 mg, 1.83 mmol) and *N*-*tert*-butyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide (685 mg, 2.02 mmol), gave methyl 3-(3'-*tert*-butylsulfamoyl-5-formyl-6-hydroxy-biphenyl-3-yl)-propionate (515 mg, 70%).

[0193] Proceeding as in Reference 14, but substituting methyl 3-formyl-4-(2-methoxy-ethoxymethoxy)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylacetate (1.8 g, 4.5 mmol) and 3-bromo-4-(2-methoxy-ethoxymethoxy)-benzonitrile (1.37 g, 4.95 mmol) gave methyl 2-[5'-cyano-5-formyl-6,2'-bis-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate (1.12 g, 50%).

[0194] Proceeding as in Reference 14, but substituting 4-(2-methoxy-ethoxymethoxy)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile (0.1 M, 87 mL, 8.71 mmol) and methyl 4-benzyloxy-3-bromo-5-formyl-benzoate (3.04 g 8.71 mmol), gave methyl 6-benzyloxy-5'-cyano-5-formyl-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl-carboxylate (1.93 g, 47%) as a yellowish solid. LCMS: ($^+$ Q + Na $^+$) 498.2 (obs.); Q (calc.) 475.16. HPLC (C-18 reverse phase) 4.262 min (1-90S).

[0195] Proceeding as Reference 14, but substituting 3-bromo-4-methoxyphenylsulfonamide (0.55 g, 2.07 mmol) and [3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)phenylacetate was added (20.7 mL, 0.1 M in toluene), gave methyl 2-[5-formyl-2'-methoxy-6-(2-methoxyethoxymethoxy)-5'-sulfamoylbiphenyl-3-yl]acetate (0.64 g, 66%).

[0196] Proceeding as in Reference 14, but substituting 2-bromo-1-(2-methoxyethoxymethoxy)-4-[2-(2-methoxyethoxy-methoxy)ethyl]benzene (0.50 g, 1.3 mmol) and methyl [3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenylacetate (13 mL, 0.1 M in toluene), gave methyl 2-[5-formyl-6,2'-bis(2-methoxyethoxymethoxy)-5'-[2-(2-methoxy-ethoxymethoxy)ethyl]-biphenyl-3-yl]acetate (0.50 g, 65%).

[0197] Proceeding as in Reference 14, but substituting 1-[3-bromo-4-(2-methoxyethoxymethoxy)benzyl]-3-methylurea (0.50 g, 1.44 mmol) and methyl [3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)]phenylacetate (14.4L, 0.10 M in toluene), gave methyl 2-[5'-formyl-6,2'-bis(2-methoxyethoxymethoxy)-5'-(3-methylureido)methyl]biphenyl-3-yl} acetate.

[0198] Proceeding as in Reference 14, but substituting 3-bromo-4-(2-methoxyethoxymethoxy)acetophenone (0.50 g, 1.65 mmol) and methyl [3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)]phenylacetate (16.5 mL, 0.10 M in toluene), gave methyl 2-[5'-acetyl-5-formyl-6,2'-bis(2-methoxyethoxymethoxy)biphenyl-3-yl]acetate (0.66 g, 79%).

[0199] Proceeding as in the above reference, but substituting *N*-[3-bromo-4-(2-methoxyethoxymethoxy)-benzyl]-acetamide and methyl [3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)]phenylacetate (20 mL, 0.10 M in toluene), gave methyl 2-[5'-(acetylaminomethyl)-6, 2'-bis(2-methoxyethoxymethoxy)-5-formylbiphenyl-3-yl]acetate (0.211 g, 20%).

[0200] Proceeding as in the above reference, but substituting methyl 4-benzyloxy-3-bromo-5-formylbenzoate (1.0 g, 2.71 mmol) and 2-(5-fluoro-2-methoxy-phenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (0.691 g, 4.16 mmol), gave methyl 6-benzyloxy-5'-fluoro-5-formyl-2'-methoxy-biphenyl-3-carboxylate (0.620 g, 57%).

[0201] Proceeding as in the above reference, but substituting methyl 3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)]phenylacetate (39 mL, 3.9 mmol) and 1-[3-bromo-4-(2-methoxyethoxymethoxy)-benzyl]-3-*tert*-butyl-urea (1.5 gm, 3.9 mmol) (prepared as described above using *tert*-butylisocyanate), gave methyl 2-[5'-(3-*tert*-butyl-ureidomethyl)-5-formyl-6,2'-bis(2-methoxyethoxymethoxy)-biphenyl-3-yl]-acetate (1.1 gm). MS LCMS 613 (M+23).

[0202] Proceeding as in the above reference, but substituting methyl 3-[3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)]phenylpropionate (3 mL, 3 mmol) and 1-[3-bromo-4-(2-methoxyethoxymethoxy)-benzyl]-3-*tert*-butyl-urea (1.0 gm, 3 mmol), gave methyl 3-[5'-(3-*tert*-butyl-ureidomethyl)-5-formyl-6,2'-bis(2-methoxyethoxymethoxy)-biphenyl-3-yl]-propionate (1 gm). MS LCMS Q⁺ 627 (M+23).

[0203] Proceeding as in the above reference, but substituting methyl 2-[3-formyl-4-(2-methoxyethoxymethoxy)-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)]phenylacetate and 3-bromo-4-(2-methoxyethoxymethoxy)-benzamide, gave methyl 2-[5'-carbamoyl-5-

formyl-6,2'-bis-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate (23%). (LCMS, M+23 528.3).

[0204] Proceeding as in the above reference, but substituting methyl 2-(3-bromo-5-formyl-4-hydroxy-phenyl)-2-methyl-propionate (0.3 g, 1 mmol) and 5-fluoro-2-methoxymethoxy-benzeneboronic acid (0.25, 1.25 mmol), gave methyl 2-(5'-fluoro-5-formyl-6-hydroxy-2'-methoxymethoxy-biphenyl-3-yl)-2-methyl-propionate (0.18 g, 48%).

[0205] Proceeding as in the above reference, but substituting methyl 2-[3-bromo-5-formyl-4-(hydroxy)-phenyl]-2-methyl-propionate (0.3 g, 1 mmol) and 4-(2-methoxy-ethoxymethoxy)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzonitrile (0.5, 1.5 mmol), gave methyl 2-[5'-cyano-5-formyl-6-hydroxy-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-2-methyl-propionate.

[0206] REFERENCE 15

Methyl 2-[5'-(*N*-tert-butylsulfamoyl)-5-formyl-6,2'-dimethoxybi-phenyl-3-yl]-2-methylpropionate

[0207] 5-tert-Butylsulfamoyl-2-methoxyphenylboronic acid (4.08 g, 14.3 mmol) was dissolved in methanol (36 mL) and the solution then was charged with methyl 2-(3-bromo-5-formyl-4-methoxyphenyl)-2-methyl-propionate (3.0 g, 9.5 mmol) as a solution in toluene (90 mL). Potassium carbonate (2N, 7.14 mL, 14.28 mmol) was added and the mixture was subjected to bubbling nitrogen for several minutes. Tetrakis palladium (1.10 g, 0.95 mmol) was added and the mixture was refluxed for 3.5 hours.

[0208] The mixture was cooled and then poured into DCM and washed several times with 5% citric acid. Chromatography over 180 g of silica (40% EtOAc/hexane) and evaporation gave methyl 2-[5'-(*N*-tert-butylsulfamoyl)-5-formyl-6,2'-dimethoxybi-phenyl-3-yl]-2-methylpropionate (3.79 g, 84%).

[0209] REFERENCE 16

Methyl 4-benzyloxy-3-bromo-5-formyl-benzoate

[0210] A mixture of 4-hydroxymethylbenzoate (64.8 g, 0.426 mol, 1.0 eq.) and acetonitrile (1 L) was stirred at room temperature while triethylamine (119 mL, 86.2 g, 0.852 mol, 2.0 eq.), magnesium chloride (60.8 g, 0.639 mol, 1.5 eq.) and paraformaldehyde (38.3 g, 1.28 mol, 3.0 eq.) were added sequentially. The mixture was heated at 80 to 82°C and monitored by HPLC. Further quantities of magnesium chloride (20.3 g) and paraformaldehyde (20 g)

were added at 1.5 and 3.5 hours each. The mixture was heated a total of 19 hours and then concentrated. The residue was combined with ethyl acetate (500 mL) and 1M hydrochloric acid (1 L) added and the mixture stirred until a solution was obtained. The aqueous layer was separated and extracted with ethyl acetate (500 mL) and the combined organic phases were washed with 1M hydrochloric acid (500 mL) and then brine, dried (MgSO_4) and concentrated. Purification of the product from the residue by filtration chromatography through silica gel (1000 mL), eluting first with DCM (3×1 L) and then 2% MeOH / DCM (3×1 L), gave methyl 3-formyl-4-hydroxy-benzoate (41.2 g, 54%) as a white solid. RP-HPLC (10-95S) RT = 3.30 min; ^1H NMR (400 MHz, d_6 -DMSO): δ 11.54* (1H, s), 10.70 (1H, s), 8.22 (1H, d, $J = 2.0$ Hz), 8.03 (1H, dd, $J = 8.0, 2.0$ Hz), 7.08 (1H, dd, $J = 8.0, 2.0$ Hz), 3.82 (3H, s); m/z (LCMS-ESI): Q^- 179 (M-H).

[0211] A mixture of the 3-formyl-4-hydroxy-benzoate (41.2 g, 0.223 mol, 1.0 eq.) and *N,N*-dimethylformamide (225 mL) was cooled to 0°C and *N*-bromosuccinimide (39.6 g, 1.0 eq.) was added in a single portion to the mixture. The mixture was cooled for 10 minutes and then allowed to stir at room temperature for 30 minutes. The mixture was poured into water (1.8 L), upon which a white precipitate formed. The precipitate was collected and washed with water (~ 2 L). Drying the damp solid azeotropically with toluene gave 3-bromo-5-formyl-4-hydroxy-benzoic acid methyl ester (52.2 g, 89%) as an off-white solid. RP-HPLC (10-95S) RT = 4.50 min. ^1H NMR (400 MHz, d_6 -DMSO): δ 10.12 (1H, s), 8.32 (1H, d, $J = 2.0$ Hz), 8.28 (1H, d, $J = 2.0$ Hz), 3.85 (3H, s).

[0212] A mixture of 3-bromo-5-formyl-4-hydroxy-benzoic acid methyl ester (26.0 g, 100 mmol, 1.0 eq) and *N,N*-dimethylformamide (400 mL) was stirred at room temperature while potassium carbonate (20.73 g, 150 mmol, 1.5 eq.) and then benzyl bromide (15 mL, 21.6 g, 125 mmol, 1.25 eq.) in a single portion was added to the mixture. The reaction mixture was stirred for 24 hours and then poured into water (1 L). The precipitate was collected by filtration and the filtrate extracted with diethyl ether ($\times 3$). The precipitate was dissolved with the ether extracts and the solution was washed with water and then brine, dried (MgSO_4) and concentrated. Purification of product from the residue via filtration chromatography on a silica gel plug (1 L), loaded in 25% DCM / Hexane and eluted successively with 1 L portions of 25 % DCM / Hexane ($\times 2$), then 50 % DCM / Hexane ($\times 1$) and finally 100% DCM ($\times 3$), gave methyl 4-benzyloxy-3-bromo-5-formyl-benzoate (25.2 g, 72%) as an off-white solid. RP-HPLC (10-95S) RT = 4.47 min; ^1H NMR (400 MHz, d_6 -DMSO): δ 10.00 (1H, s), 8.42 (1H, d, $J = 2.0$ Hz), 8.21 (1H, d, $J = 2.0$ Hz), 3.88 (3H, s); m/z (LCMS-ESI): Q^+ 371/373 (M+Na).

[0213] REFERENCE 17

N-tert-Butyl-4-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide

[0214] A 500 mL 3-necked flask, equipped with thermometer, overhead stirrer and a 60 mL dropping funnel, was charged with 2-bromoanisole (46.8 g, 0.25 mol, 1.0 eq.) and anhydrous chloroform (250 mL). The flask was flushed with nitrogen and cooled with a brine-ice cool-bath to an internal temperature of -7°C and then chlorosulfonic acid (87.4 g, 0.75 mol, 3.0 eq.) was added via dropping funnel over 1 hour while maintaining an internal temperature of less than -5°C. The reaction mixture was stirred for 50 minutes and then poured on to ice (500 g). The mixture was stirred until the ice melted and then the organic layer was separated and washed with water (2 x 200 mL). The combined aqueous layers were backwashed with chloroform (2 x 200 mL) and the combined organic phases were washed with brine and dried (MgSO₄).

[0215] The organic phase was treated at room temperature with triethylamine (87 mL, 63 g, 0.625 mol, 2.5 eq.) and then *tert*-butylamine (34 mL, 24 g, 0.325 mol, 1.3 eq.). The reaction mixture was stirred overnight, cooled in an ice-bath and poured into ice cold 2M hydrochloric acid (500 mL). The organic layer was separated and washed with 2M hydrochloric acid (2 x 250 mL) and brine, dried (MgSO₄) and concentrated. Crystallization of the residue from chloroform-hexane gave 3-bromo-*N-tert*-butyl-4-methoxy-benzenesulfonamide (37.5 g, 47%) as brilliant white crystals. RP-HPLC (10-95S) RT = 3.92 min. ¹H NMR (400 MHz, d₆-DMSO): δ 7.94 (1H, d, J = 2.4 Hz), 7.77 (1H, dd, J = 8.8, 2.4 Hz), 7.48 (1H, s), 7.25 (1H, d, 8.8 Hz), 3.92 (3H, s), 1.08 (9H, s).

[0216] A mixture of 3-bromo-*N-tert*-butyl-4-methoxy-benzenesulfonamide (36.2 g, 112 mmol, 1.0 eq), bis(pinacolato)diborane (30.0 g, 117 mmol, 1.05 eq.), potassium acetate (33.0 g, 336 mmol, 3.0 eq.) and PdCl₂(dppf)·DCM (533 mg, 0.653 mmol, 5.8 mol %, in 115 mL of 1,4-dioxane) was heated at 100 °C under nitrogen and then 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (0.35 eq.) was added to the mixture. The reaction mixture was heated for 28 hours and then allowed to cool. The mixture was filtered of solids and concentrated. The residue was dissolved in ethyl acetate (500 mL) and the solution was washed with 5% citric acid (3x 200 mL), saturated sodium bicarbonate (3 x 200 mL) and then brine, dried (MgSO₄) and concentrated. Purification of product from the residue by silica-gel chromatography, eluting with 10-50% EtOAc/Hex gave *N-tert*-butyl-4-methoxy-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzenesulfonamide (30 g, 72%) as a pale-orange solid. RP-HPLC (10-95S): RT = 3.17 min. ¹H NMR (400 MHz, d₆-DMSO): δ 7.95 (1H, d, J

= 2.4 Hz), 7.85 (1H, dd, J = 8.8, 2.4 Hz), 7.36 (1H, s), 7.11 (1H, d, J = 8.8), 3.81 (3H, s), 1.29 (12H, s), 1.07 (9H, s); m/z (LCMS-ESI): Q⁺ 310 (boronic acid+Na), 370 (M+H), 392 (M+Na); Q⁻ 354 (M-Me), 556 (boronic acid anhydride).

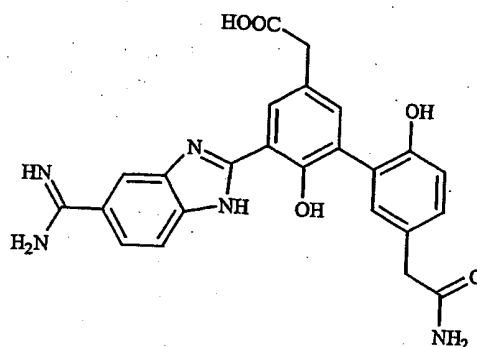
[0217] REFERENCE 18

Methyl 6-benzyloxy-5'-tert-butylsulfamoyl-5-formyl-2'-methoxy-biphenyl-3-carboxylate

[0218] A mixture of methyl 4-benzyloxy-3-bromo-5-formyl-benzoate (2.10 g, 6.00 mmol, 1.0 eq.), prepared as in Reference 16, *N*-tert-butyl-4-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzenesulfonamide (2.44 g, 6.60 mmol, 1.1 eq.), prepared as in Reference 17, cesium carbonate (5.86 g, 18.0 mmol, 3.0 eq.) and dichlorobis(triphenylphosphine)palladium(II) (126 mg, 0.180 mmol, 3 mol %) was heated overnight in *N,N*-dimethylformamide (60 ml) at 110°C under a nitrogen atmosphere. The reaction mixture was filtered of solids and poured into 1M hydrochloric acid (600 mL). The mixture was extracted with ethylacetate (x3) and the combined organic phases were backwashed with water and then brine, dried (MgSO₄) and concentrated. The residue was dissolved in tetrahydrofuran (10 mL) and hexanes were added to the solution until precipitation began to occur. The precipitate was collected and washed with hexanes. Drying gave methyl 6-benzyloxy-5'-tert-butylsulfamoyl-5-formyl-2'-methoxy-biphenyl-3-carboxylate (492 mg, 17%) as grey/brown powder. RP-HPLC (10-95S): RT = 4.32 min. ¹H NMR (400 MHz, d₆-DMSO): δ 10.15 (1H, s), 8.27 (1H, d, J = 2.0 Hz), 8.05 (1H, d, J = 2.0 Hz), 7.90 (1H, dd, J = 8.8, 2.4 Hz), 7.78 (1H, d, J = 2.4 Hz), 7.41 (1H, s), 7.33 (1H, d, J = 8.8 Hz), 7.25-7.20 (3H, m), 7.03 (2H, dd, J = 7.6, 2.0 Hz), 4.69 (2H, s), 3.87 (3H, s), 3.81 (3H, s), 1.06 (9H, s); m/z (LCMS-ESI): Q⁺ 534 (M+Na); Q⁻ 510 (M-H).

[0219] EXAMPLE 1

Synthesis of [5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid



Step 1

[0220] Methyl 2-(5-formyl-6,2'-bis-(2-methoxy-ethoxymethoxy)-5'-{[(2-methoxy-ethoxymethyl)-carbamoyl]-methyl}-biphenyl-3-yl)-acetate (1.34 g, 2.58 mmol, 1.0 eq.), was dissolved in methanol (13 mL) and the solution was charged with 3,4-diaminobenzamidine hydrochloride (0.58 g, 3.10 mmol, 1.2 eq.) and 1,4-benzoquinone (0.28 g, 2.58 mmol, 1.0 eq.). The mixture was refluxed for seven hours and then concentrated to give methyl 2-(5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-6,2'-bis-(2-methoxy-ethoxymethoxy)-5'-{[(2-methoxy-ethoxymethyl)-carbamoyl]-methyl}-biphenyl-3-yl)-acetate as a crude product. LCMS: Calcd 665.

Step 2

[0221] Methyl 2-(5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-6,2'-bis-(2-methoxy-ethoxymethoxy)-5'-{[(2-methoxy-ethoxymethyl)-carbamoyl]-methyl}-biphenyl-3-yl)-acetate was dissolved in methanol (5 mL) and the solution was treated with hydrogen chloride (10 mL, 4M in dioxane). The mixture was stirred for 2 hours and then concentrated by evaporation. The residue was pumped down to give methyl 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-5'-carbamoylmethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetate.

Step 3

[0222] Methyl 2-[5-(5-Carbamidoyl-1H-benzoimidazol-2-yl)-5'-carbamoylmethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetate was dissolved in methanol (11 mL) and the solution was treated with sodium hydroxide (11 mL, 10%). The mixture was stirred for 1 hour at room temperature and then concentrated by evaporation. The residue was pumped down and prepped by preparative hplc (5, 40) acetonitrile. The desired fraction was pooled and evaporated to give 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-5'-carbamoylmethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid (50 mg). LCMS: Calcd 459; Obsd (MH⁺) 460. NMR (DMSO-d₆) δ 3.26 (s, 2H), 3.98 (m, 2H), 6.80 (s, 1H), 6.83 (d, J = 9 Hz, 1H), 7.07 (m, 2H), 7.22 (s, 1H), 7.40 (s, 1H), 7.72 (d, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.98 (s, 1H), 8.16 (s, 1H), 8.96 (s, 2H), 9.36 (s, 2H).

[0223] Proceeding as in Example 1, but substituting 2-[3'-*tert*-butylsulfamoyl-5-formyl-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetic acid methyl ester (410 mg, 0.83 mmol) and 3,4-diaminobenzamidine hydrochloride (170 mg, 0.91 mmol) and then deprotecting first with hydrogen chloride in dioxane and methanol and subsequently with 1*N* aqueous hydrochloric acid in acetonitrile, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid (97 mg, 25%) as a beige amorphous powder. MS *m/z*: 466.1 ($M+H^+$) and 464.2 ($M-H^+$). 1H NMR (400 MHz, DMSO- d_6): δ 9.31 (bs, 2H), 8.90 (bs, 2H), 8.22 (s, 1H), 8.07 (d, $J = 10$ Hz, 2H), 7.82 (dd, $J = 12, 8$ Hz, 2H), 7.73 (s, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.45 (s, 1H), 7.39 (s, 1H) and 3.67 (s, 2H).

[0224] Proceeding as in Example 1, but substituting 2-[5-formyl-6-(2-methoxy-ethoxymethoxy)-3'-methylsulfamoyl-biphenyl-3-yl]-acetic acid methyl ester (550 mg, 1.22 mmol) and 3,4-diaminobenzamidine hydrochloride (250 mg, 1.34 mmol) and then deprotecting with 1*N* aqueous hydrochloric acid in acetonitrile, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid (122 mg, 21%) as a light beige amorphous powder. MS *m/z*: 480.4 ($M+H^+$) and 478.2 ($M-H^+$). 1H NMR (400 MHz, DMSO- d_6): δ 9.34 (bs, 2H), 8.96 (bs, 2H), 8.18 (s, 1H), 8.07 (d, $J = 10$ Hz, 2H), 7.88 (d, $J = 8$ Hz, 2H), 7.70 (m, 3H), 7.51 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.48 (s, 1H), 7.39 (s, 1H) and 3.67 (s, 2H) and 2.46 (d, $J = 10$ Hz, 3H).

[0225] Proceeding as in Example 1, but substituting 2-(3'-*tert*-butylsulfamoyl-5-formyl-6-hydroxy-biphenyl-3-yl)-2-methyl-propionic acid methyl ester (280 mg, 0.64 mmol) and 3,4-diaminobenzamidine hydrochloride (150 mg, 0.71 mmol) and then first deprotecting with trifluoroacetic acid and subsequently deprotecting with 1*N* aqueous hydrochloric acid in acetonitrile, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]-2-methylpropionic acid (5 mg, 2.1%) as a light red amorphous powder. MS *m/z*: 494.4 ($M+H^+$) and 492.5 ($M-H^+$). 1H NMR (400 MHz, DMSO- d_6): δ 9.32 (bs, 2H), 8.94 (bs, 2H), 8.22 (s, 1H), 8.08 (d, $J = 10$ Hz, 2H), 7.88 (d, $J = 8$ Hz, 2H), 7.70 (m, 3H), 7.51 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.48 (s, 1H), 7.39 (s, 1H) and 2.37 (s, 6H).

[0226] Proceeding as in Example 1, but substituting 3-(3'-*tert*-butylsulfamoyl-5-formyl-6-hydroxy-biphenyl-3-yl)-propionic acid methyl ester (515 mg, 1.23 mmol) and 3,4-diaminobenzamidine hydrochloride (280 mg, 1.47 mmol) and then first deprotecting with trifluoroacetic acid and subsequently deprotecting with 1*N* aqueous hydrochloric acid in acetonitrile, gave 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-aminosulfonylbiphenyl-3-yl]-propionic acid (266 mg, 45%) as an off-white amorphous powder. MS *m/z*: 480.2 ($M+H^+$) and 478.2 ($M-H^+$). 1H NMR (400 MHz, DMSO- d_6): δ 9.32 (bs, 2H), 8.90 (bs, 2H), 8.23 (s, 1H), 8.09 (d, $J = 10$ Hz, 2H), 7.82 (m, 2H), 7.73 (d, $J = 8.8$

Hz, 3H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.42 (s, 1H), 7.39 (s, 1H), 2.91 (t, $J = 7.7$ Hz, 1H) and 2.67 (t, $J = 7.7$ Hz, 1H).

[0227] Proceeding as in Example 1, but substituting methyl 2-[5-formyl-2'-methoxy-6-(2-methoxyethoxymethoxy)-5'-sulfamoylbiphenyl-3-yl]acetate (0.55 g, 1.1 mmol) and 3,4-diaminobenzamidine hydrochloride (1.25 mmol, 0.23 g) and then deprotecting first with hydrogen chloride in dioxane and methanol and subsequently deprotecting with pyridine hydrochloride to give 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-aminosulfonylbiphenyl-3-yl]acetic acid (0.31 g, 59 %). LCMS: Calcd 481.49; Obsd (MH⁺) = 482.0, (MH⁻) = 480.2. NMR (DMSO-*d*₆) δ 3.621 (s, 2H), 7.07 (d, $J = 8$ Hz, 1H), 7.15 (br s, 2H), 7.27 (d, $J = 2$ Hz, 1H), 7.63 (d, $J = 2$ Hz, 1H), 7.65 (m, 2H), 7.73 (d of d, $J = 2$, $J = 8$ Hz, 1H), 7.83 (d, $J = 8$ Hz, 1H), 8.08 (d, $J = 2$ Hz, 1H), 8.17 (s, 1H), 9.10, 9.39 (2s, 4H).

[0228] Proceeding as in Example 1, but substituting methyl 2-{5-formyl-6,2'-bis(2-methoxyethoxymethoxy)-5'-[2-(2-methoxy-ethoxymethoxy)ethyl]biphenyl-3-yl}acetate (0.50 g, 0.84 mmol) and 3,4-diaminobenzamidine hydrochloride (0.187 g, 1.0 mmol) and then deprotecting first with hydrogen chloride in dioxane and methanol and subsequently deprotecting with 3M aqueous hydrochloric acid in acetonitrile, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-(2-hydroxyethyl)biphenyl-3-yl]acetic acid (137 mg, 37%). LCMS: Calcd 446.45; Obsd (MH⁺) 447.2, (MH⁻) 445.3. NMR (DMSO-*d*₆) δ 2.64 (t, $J = 7$ Hz, 2H), 3.56 (t, $J = 7$ Hz, 2H), 3.58 (s, 2H), 6.81 (d, $J = 9$ Hz, 1H), 7.00 (d, $J = 2$ Hz, 2H), 7.24 (s, 1H), 7.71 (d, $J = 9$ Hz, 1H), 7.82 (d, $J = 9$ Hz, 1H), 7.97 (s, 1H), 8.96, 9.33 (2s, 4H).

[0229] Proceeding as in Example 1, but substituting methyl 2-{5-formyl-6,2'-bis(2-methoxyethoxymethoxy)-5'-[(3-methylureido)methyl]biphenyl-3-yl}acetate and 3,4-diaminobenzamidine-HCl (0.306 g, 1.64 mmol) and then deprotecting first with hydrogen chloride in dioxane and methanol and subsequently deprotecting with lithium hydroxide in water, gave 2-{5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-[(3-methylureido)methyl]biphenyl-3-yl}acetic acid (17 mg). LCMS: Calcd 488.49; Obsd (MH⁺) 489.2, (MH⁻) 487.3.

[0230] Proceeding as in Example 1, but substituting methyl 2-[5'-acetyl-5-formyl-6,2'-bis(2-methoxyethoxymethoxy)bi-phenyl-3-yl]acetate (0.66 g, 1.3 mmol) and 3,4-diaminobenzamidine hydrochloride (0.29 g, 1.56 mmol) and then deprotecting first with trifluoroacetic acid and subsequently deprotecting with aqueous hydrochloric acid in acetonitrile, gave 2-[5'-acetyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-yl]acetic acid (215 mg, 37%). LCMS: Calcd 444.44; Obsd (MH⁺) 445.3, (MH⁻)

443.0. NMR (DMSO- d_6) δ 2.79 (s, 3H), 3.62 (s, 2H), 7.04 (d, $J=8$ Hz, 1H), 7.29 (d, $J=1$ Hz), 7.73 (d, $J=8$ Hz, 1H), 7.82 (m, 3H), 8.06 (s, 1H), 8.17 (s, 1H), 9.09, 9.38 (2s, 4H).

[0231] Proceeding as in Example 1, but substituting methyl 2-[5'-(acetylaminomethyl)-6, 2'-bis(2-methoxyethoxymethoxy)-5-formylbiphenyl-3-yl]acetate (0.21 g, 0.39 mmol) and 3,4-diaminobenzamidine-HCl (88.0 mg, 0.47 mmol) and then deprotecting first with hydrogen chloride in dioxane and methanol and subsequently with sodium hydroxide solution in methanol, gave 2-[5'-(acetylaminomethyl)-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxybiphenyl-3-yl]acetic acid (4.1 mg, 2.2%). LCMS: Calcd 473.48; Obsd (MH⁺) 474.1, (MH⁻) 472.1.

[0232] Proceeding as in Example 1, but substituting methyl 2-[5'-(3-*tert*-butyl-ureidomethyl)-5-formyl-6,2'-bis(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetic acid methyl ester (0.7 g, 1.1 mmol) and diaminobenzamidine hydrochloride (0.331 g, 1.8 mmol) and then deprotecting first with hydrogen chloride in dioxane, second with trifluoroacetic acid and finally with aqueous sodium hydroxide solution in methanol, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-ureidomethyl-biphenyl-3-yl]-acetic acid hydrochloride (45 mg). MS LCMS 475.2 (M+1). ¹H-NMR (d_6 -DMSO) δ ppm: 3.53 (2 H, s), 4.0 (2 H, s), 6.77 (1 H, d, $J=8.8$ Hz), 6.98 (2 H, m), 7.15 (1 H, d, $J=2$ Hz), 7.63 (1 H, d, $J=8.9$ Hz), 7.76 (1 H, br s), 7.89 (1 H, m), 8.09 (1 H, br s), 8.79 (2 H, br s) and 9.23 (2 H, br s).

[0233] Proceeding as in Example 1, but substituting 3-[5'-(3-*tert*-butyl-ureidomethyl)-5-formyl-6,2'-bis(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-propionic acid methyl ester (775 mg, 1.9 mmol) and diaminobenzamidine hydrochloride (428 mg, 2.29 mmol) and then deprotecting first with hydrogen chloride in dioxane, second with trifluoroacetic acid and finally with aqueous sodium hydroxide solution in methanol, gave 3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-ureidomethyl-biphenyl-3-yl]-propionic acid hydrochloride (65 mg). MS LCMS Q⁺ 489.2 (M+1). ¹H-NMR (d_6 -DMSO) δ ppm: 3.58 (2 H, s), 3.65 (2 H, s), 4.03 (2 H, s), 6.78 (1 H, dd, $J=8.8$ and 2.4 Hz), 6.97 (2 H, m), 7.16 (1 H, d, $J=2.0$ Hz), 7.65 (1 H, d, $J=7.2$ Hz), 7.76 (1 H, d, $J=8.4$ Hz), 7.92 (1 H, d, $J=2$ Hz), 8.09 (1 H, br s), 8.88 (2 H, br s) and 9.26 (2 H, br s).

[0234] Proceeding as in Example 1, but substituting 2-[5'-carbamoyl-5-formyl-6,2'-bis(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetic acid methyl ester (0.098g, 0.19 mmol) and 3,4-diaminobenzamidine and then deprotecting with hydrogen chloride in dioxane and subsequently with aqueous sodium hydroxide solution in methanol, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid (12 mg, 14%). ¹H NMR (DMSO- d_6) δ 9.36 (br s, 2), 9.09 (br s, 2), 8.18 (s, 1),

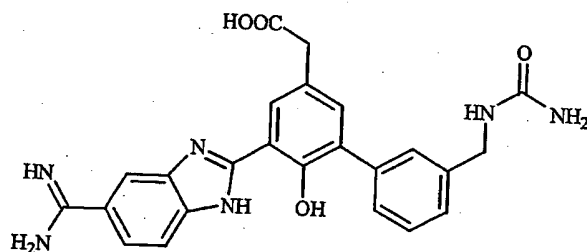
8.04 (s, 1), 7.89 (d, 1, $J=7.8$ Hz), 7.80-7.68 (m, 4), 7.29 (s, 1), 7.08 (br s, 1), 6.97 (d, 1, $J=7.8$ Hz), 3.65 (br s, water), 2.49 (DMSO).

[0235] Proceeding as in Example 1, but substituting 2-(5'-fluoro-5-formyl-6-hydroxy-2'-methoxymethoxy-biphenyl-3-yl)-2-methyl-propionic acid methyl ester (0.18 g, 0.4 mmol) and 3,4-diaminobenzamidine hydrochloride (0.11 g (0.6 mmol) and then first deprotecting with hydrogen chloride in dioxane and ethanol and subsequently deprotecting with hydrochloric acid in acetonitrile, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-2-methyl-propionic acid (0.035 g). MS: found ($M+H^+$) 449.0, ($M-H^+$) 447.3, calc. 448.15.

[0236] Proceeding as in Example 1, but substituting 2-[5'-cyano-5-formyl-6-hydroxy-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-2-methyl-propionic acid methyl ester and 3,4-diaminobenzamidine hydrochloride and then deprotecting with hydrogen chloride in dioxane and methanol, gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-cyano-6,2'-dihydroxy-biphenyl-3-yl]-2-methyl-propionic acid methyl ester.

[0237] EXAMPLE 2

Synthesis of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-ureidomethyl-biphenyl-3-yl]-acetic acid



Step 1

[0238] 2-[3'-(tert-Butoxycarbonylamino-methyl)-5-formyl-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetic acid (0.6503 g, 1.334 mmol, 1.0 eq.) was dissolved in methanol (10 mL) and the solution was charged with 3,4-diaminobenzamidine hydrochloride (0.298 g, 1.601 mmol, 1.2 eq.) and 1,4-benzoquinone (0.1442 g, 1.334 mmol, 1.0 eq.). The mixtures was refluxed for 4 hours and 15 minutes and then concentrated by evaporation to give methyl 2-[3'-(tert-butoxycarbonylamino-methyl)-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate. LCMS: Calcd 617; Obsd (MH^+) 618.

Step 2

[0239] Methyl 2-[3'-(*tert*-butoxycarbonylamino-methyl)-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate was dissolved in methanol (10 mL) and the solution was treated with hydrogen chloride (10 mL, 4M in dioxane). The mixture was stirred for 2 hours and then concentrated by evaporation. The residue was pumped down to give methyl 2-[3'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-acetate. LCMS: Calcd 429; Obsd (MH⁺) 430.

[0240] Step 3

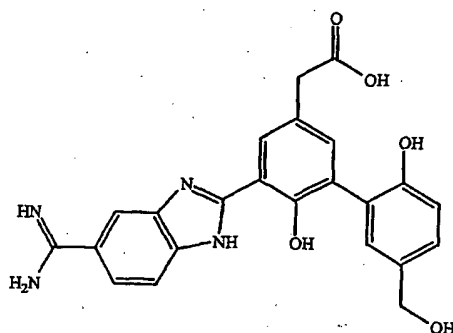
[0241] Methyl 2-[3'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-acetate was dissolved in methanol (11 mL) and the solution was treated with sodium hydroxide (11 mL, 10%). The mixture was stirred for 1 hour at room temperature and then concentrated by evaporation. The residue was pumped down to give 2-[3'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-acetic acid. LCMS: Calcd 415; Obsd (MH⁺) 416.

Step 4

[0242] 2-[3'-Aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-biphenyl-3-yl]-acetic acid (0.6 g, 1.44 mmol, 1.0 eq.) was dissolved in methanol (10 mL) and the solution was charged with potassium cyanate (0.82 g, 10.11 mmol, 7.0 eq.), triethylamine (0.88 g, 8.67 mmol, 6.0 eq., 1.21 mL) and water (8 mL). The mixture was heated at 50 °C overnight. The product then was prepped by preparative hplc (5, 40) acetonitrile. The desired fraction was pooled and evaporated to give 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-3'-ureidomethyl-biphenyl-3-yl]-acetic acid (1.4 mg). LCMS: Calcd 458; Obsd (MH⁺) 459.

[0243] EXAMPLE 3

Synthesis of [5-(5-Carbamidimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-hydroxymethyl-biphenyl-3-yl]-acetic acid



Step 1

[0244] Methyl 2-[2'-cyano-5-formyl-6,5'-bis-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate (400 mg, 0.82 mmol), 3,4-diaminobenzamidine hydrochloride (168 mg, 0.9 mmol) and 1,4-benzoquinone (88 mg (0.86 mmol) were dissolved in methanol (40 mL) and the mixture was refluxed for thirty minutes. The solvent was removed by rotary evaporation to give methyl 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-5'-cyano-6,2'-bis-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate.

Step 2

[0245] Methyl 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-5'-cyano-6,2'-bis-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl]-acetate was dissolved in hydrogen chloride (5 mL, 4N in dioxane) and dry methanol (5 mL) and the solution was stirred for 1 hour. The solvent was evaporated under reduced pressure and the residue dried on high vacuum overnight to give methyl 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-5'-cyano-6,2'-dihydroxy-biphenyl-3-yl]-acetate.

Step 3

[0246] A mixture of the methyl 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-5'-cyano-6,2'-dihydroxy-biphenyl-3-yl]-acetate, aqueous sodium hydroxide (5 mL, 1N) and methanol (5 mL) was stirred at room temperature for 1 hour. Solvents were evaporated to give 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-5'-cyano-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid.

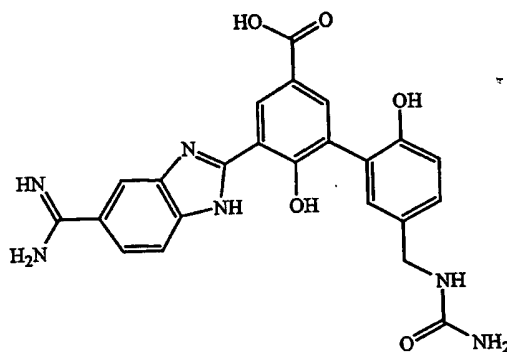
Step 4

[0247] 2-[5-(5-Carbamidoyl-1H-benzoimidazol-2-yl)-5'-cyano-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid was combined with water (10 mL), aqueous hydrochloric acid (5.2 mL, 1N) and Pearlman's catalyst (100 mg) and the mixture was stirred under 1 atmosphere of hydrogen for 6 hours. The solution was filtered through celite and product purified by reverse phase preparative HPLC (0.02 N HCl / ACN gradient) to give 2-[5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-hydroxymethyl-biphenyl-3-yl]-acetic acid (28 mg, 8%) as a light brown amorphous powder. MS m/z : 433.4 ($M+H^+$) and 431.2 ($M-H^+$). 1H NMR (d_6 -DMSO) δ ppm: 9.32 (bs, 2H), 8.92 (bs, 2H), 8.15 (s, 1H), 8.03

(s, 1H), 7.83 (d, $J = 7.7$ Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.25 (s, 1H), 7.11 (d, $J = 7.2$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 1H), 3.65 (s, 2H), 2.64 (dd, $J = 17.1$ Hz, 1.9 Hz, 2H).

[0248] EXAMPLE 4

Synthesis of 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-ureidomethyl-biphenyl-3-carboxylic acid



Step 1

[0249] 3, 4-Diaminobenzamidine hydrochloride (0.185 g, 0.99 mmol) was added to a solution of methyl 6-benzyloxy-5'-cyano-5-formyl-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-yl-carboxylate (0.394 g, 0.83 mmol) in methanol (100 mL) and the mixture was heated overnight at 70 °C to give methyl 6-benzyloxy-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-cyano-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-carboxylate. LCMS: ($Q + Na^+$) 627.2. HPLC (C-18 reverse phase) 3.135 min (1-1-90S).

Step 2

[0250] Pearlman's catalyst (25 mg, 5% by weight) was added to the solution of methyl 6-benzyloxy-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-cyano-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-carboxylate and the mixture was subjected to hydrogenation at 50 psi for overnight. The organic layer was concentrated to give methyl 5'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-carboxylate as a yellowish solid. LCMS: ^+Q 520.5, ^-Q 518.3. HPLC (C-18 reverse phase) 2.523 min (1-1-90S).

Step 3

[0251] Hydrochloric acid (1M) was added to the methyl 5'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6-hydroxy-2'-(2-methoxy-ethoxymethoxy)-biphenyl-3-carboxylate and the mixture was heated 4 hours and then concentrated to give 5'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-

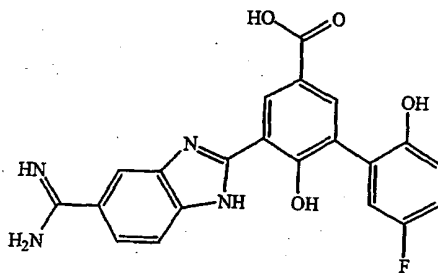
carboxylic acid as an off-white solid. LCMS: ^+Q 418.3, ^-Q 416.2. HPLC (C-18 reverse phase) 2.186 min (1-1-90S), 5.057 min (1-90).

Step 4

[0252] 5'-Aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-carboxylic acid was dissolved in methanol (5 mL) and water (5 mL). Potassium cyanate (0.673 g, 8.28 mmol) and triethylamine (0.419 g, 0.58 mL, 4.14 mmol) was added to the solution and the mixture was heated overnight at 60 °C. The mixture was concentrated and purified by reverse phase HPLC to give 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-ureidomethyl-biphenyl-3-carboxylic acid as a yellow solid (120mg, 30% yield). LCMS: ^+Q 520.5 461.0; ^-Q 459.1. HPLC (C-18 reverse phase) 2.186 min (1-1-90S), 5.132 min (1-1-90). 1H NMR (400 MHz, DMSO- d_6) δ 9.38 (br-s, 3H), 9.06 (br-s, 3H), 8.78 (d, J = 2.00, 1H), 8.18 (br-s, 1H), 7.86 (m, 3H), 7.74 (m, 2H), 7.08 (m, 3H), 6.88 (d, 2H).

[0253] EXAMPLE 5

Synthesis of 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-carboxylic acid hydrochloride



Step 1

[0254] 3, 4-Diaminobenzamidine hydrochloride (0.739 g, 3.96 mmol) was added to a solution of methyl 6-benzyloxy-5'-fluoro-5-formyl-2'-methoxy-biphenyl-3-carboxylate (1.3 g, 3.30 mmol) in methanol (100 mL) and the mixture was heated to 85°C for 3 days. The solvent then was concentrated to give methyl 6-benzyloxy-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-2'-methoxy-biphenyl-3-carboxylate.

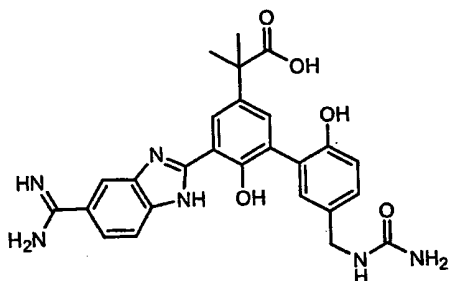
Step 2

[0255] Methyl 6-benzyloxy-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-2'-methoxy-biphenyl-3-carboxylate was dissolved in hydrobromic acid (100 mL, 48%) and the solution heated to 110 °C for 24 hours. The majority of the solvent then was evaporated off and the resulting solid was collected by filtration and the resulting solid was purified by

reverse phase HPLC to give 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-carboxylic acid hydrochloride (0.780 g, 53%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.35 (br-s, 1H), 8.94 (br-s, 1H), 8.79 (d, *J* = 2.00, 1H), 8.18 (br-s, 1H), 7.93 (d, *J* = 1.95, 1H), 7.85 (m, 1H), 7.74 (m, 2H), 7.08 (m, 2H), 6.93 (m, 1H). ESIMS *m/z*: M⁺ 407.1.

[0256] EXAMPLE 6

Synthesis of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-ureidomethyl-biphenyl-3-yl]-2-methyl-propionic acid



Step 1

[0257] Methyl 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-cyano-6,2'-dihydroxy-biphenyl-3-yl]-2-methyl-propionic acid methyl ester (0.1 g (0.21 mmol), prepared as in Example 4, was dissolved in 1N aqueous hydrochloric acid (5 mL) and methanol (15 mL) and the solution was subjected to hydrogenation at 1 atm over Pd(OH)₂ (0.03 g) for 2 hours. The mixture was filtered through celite, the solvents were removed in vacuum and the residue was triturated with ethyl ether and solids were collected by filtration to give methyl 2-[5'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-yl]-2-methyl-propionate (0.09 g).

Step 2

[0258] Methyl 2-[5'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-yl]-2-methyl-propionate was heated with aqueous hydrochloric acid (5 mL, 3N) and acetonitrile (5 mL) for 3 hours. The solvents were removed in vacuum and the residue purified by reversed phase HPLC (acetonitrile gradient) to give 2-[5'-aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-yl]-2-methylpropionic acid (0.09 g, 0.19 mmol).

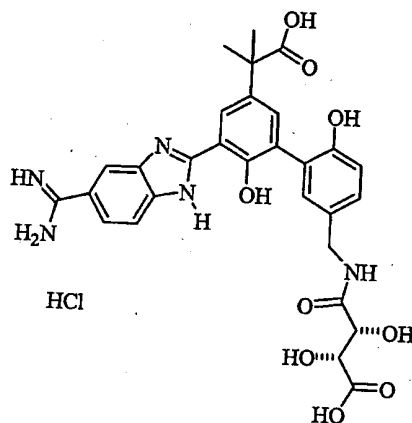
Step 3

[0259] 2-[5'-Aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-yl]-2-methylpropionic acid was dissolved in a mixture of methanol and water.

Triethylamine was added to establish pH 9 and the mixture was heated with potassium cyanate (0.08 g, 0.95 mmol) for 16 hours at 40 °C. The mixture was concentrated under reduced pressure and the residue was purified by reversed phase HPLC (acetonitrile gradient) to give 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-ureidomethyl-biphenyl-3-yl]-2-methyl-propionic acid (0.03 g). ¹H NMR (DMSO-*d*₆) : δ 1.55 (s, 6H), 4.07 (s, 2H), 6.41 (br.s, 1H), 6.82 (d, *J*=8.4 Hz, 1H), 7.00-7.04 (m, 2H), 7.26 (d, *J*=2.6 Hz, 1H), 7.75 (m, 1H), 7.85 (m, 1H), 8.07 (s, 1H), 8.99 (s, 2H), 9.29 (s, 2H). MS: found (*M*+*H*⁺) 503.2, (*M*-*H*⁺) 501.4, calcd. 502.20.

[0260] EXAMPLE 7

Synthesis of *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2,3-dihydroxy-succinamic acid hydrochloride

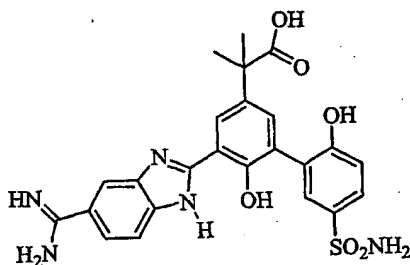


[0261] 2-[5'-Aminomethyl-5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-biphenyl-3-yl]-2-methyl-propionic acid ditrifluoroacetic acid salt (160 mg, 0.233 mmol, approx 90% purity) was dissolved in a mixture of anhydrous dimethylacetamide (4 mL) and triethylamine (0.025 mL). The solution was stirred while solid 4*R*-acetoxy-2,5-dioxo-tetrahydro-furan-3*R*-yl acetate (52 mg, 0.24 mmol) and additional triethylamine (0.045 mL) was added. The mixture was stirred at ambient temperature for 70 minutes and then cooled on ice bath. Concentrated aqueous ammonia 4 mL was added dropwise to the mixture. The mixture was stirred in a tightly closed flask for 1 day at ambient temperature and then concentrated by evaporation to dryness on highvac. The residue was treated with acetonitrile (15 mL) and an obtained precipitate was collected by filtration, washed with acetonitrile and dissolved in a mixture of water (50 mL), methanol (20 mL) and

trifluoroacetic acid (1 mL). The solution was filtered and concentrated by evaporation to dryness. The residue was purified on a preparative reverse-phase HPLC [C-18 column in a water (+conc. HCl 1.75 mL/L)/acetonitrile, 2-25%] and the pure product lyophilized to give *N*-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid mono-hydrochloride salt (52 mg, 39% yield) as a pale yellow amorphous solid. MS/ES+: $M+1=592$, MS/ES-: $M-1=590$. $^1\text{H-NMR}$ ($^d\text{DMSO}$, 400MHz): δ 9.337 (br s, 2H), 8.962 (br s, 2H), 8.163 (br s, 1H), 8.118 (br d, $J=2.3\text{Hz}$, 1H), 8.077 (app t, $J=5.9\text{Hz}$, 1H), 7.842 (br d, $J=9.0\text{Hz}$, 1H), 7.717 (br d, $J=8.2\text{Hz}$, 1H), 7.285 (d, $J=2.3\text{Hz}$, 1H), 7.101 (m, 2H), 6.837 (app d, $J=8.6\text{Hz}$, 1H), 4.356 (br d, $J=1.9\text{Hz}$, 1H), 4.228 (m, 2H), 1.581 (s, 6H).

[0262] EXAMPLE 8

Synthesis of 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid

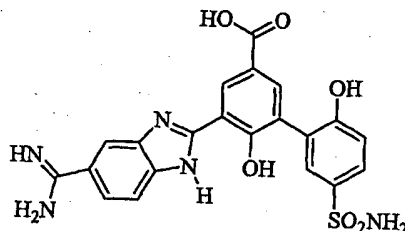


[0263] Methyl 2-[5'-(*N*-tert-butylsulfamoyl)-5-formyl-6,2'-dimethoxybiphenyl-3-yl]-2-methylpropionate (3.79 g, 7.94 mmol), prepared as in Reference 15, was dissolved in methanol (150 mL) and then 3,4-diaminoamidinobenzene hydrochloride (1.50 g, 8.0 mmol) and 1,4-benzoquinone (0.865 g) were added to the solution. The mixture was refluxed for 6 hours, cooled and then concentrated by evaporation. The residue was treated with trifluoroacetic acid (≈ 35 mL) and the mixture was stirred for approximately 1.5 hours and then concentrated by evaporation under vacuum. The residue was subjected to pyridine hydrochloride (22 g) heated at 180°C for 3 hours. The mixture then was cooled and dissolved in water with minimal acetonitrile. Purification gave 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid (3.57 g, 82%). LCMS: Calcd 509.54; Obsd (MH+) 510.4, (MH-) 508.1. NMR ($\text{DMSO-}d_6$) δ 1.60 (s, 6H), 7.08 (d, $J=7\text{ Hz}$, 1H), 7.21 (s, 2H), 7.16 (d, $J=2\text{ Hz}$, 1H),

7.66 (d, $J = 7$ Hz, 1H), 7.69 (d, $J = 2$ Hz, 1H), 7.76 (d of d, $J = 2, 7$ Hz, 1H), 7.84 (d, $J = 7$ Hz, 1H), 8.21 (d, $J = 2$ Hz, 2H), 8.99 (s, 2H), 9.39 (s, 2H), 10.16 (br s, 1H).

[0264] EXAMPLE 9

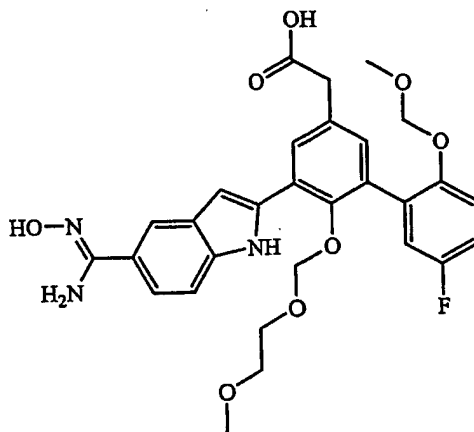
Synthesis of 5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid hydrochloride



[0265] Methyl 6-benzyloxy-5'-tert-butylsulfamoyl-5-formyl-2'-methoxy-biphenyl-3-carboxyate (300 mg, 0.587 mmol, 1.0 eq.), prepared as in Reference 18, and 3,4-diaminobenzamidine hydrochloride (109 mg, 0.587 mmol, 1.0 eq.) was dissolved in methanol and the mixture was heated for 2 days at reflux under air. The reaction mixture was concentrated and the residue suspended in 2M hydrochloric acid. The suspension was heated at 100°C for 3 days and then concentrated via a toluene azeotrope. The residue was combined with an excess of pyridine hydrochloride (10-40 eq) and the mixture was heated at 185°C until the reaction had completed. The mixture then was taken up in 10 mM hydrochloric acid and the mixture was loaded directly onto a C-18 plug and gradient eluted with 0-50% MeCN/10 mM HCl. Fractions containing product were initially concentrated under reduced pressure and then by lyophilization to give 5-(5-carbamimidoyl-1H-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid hydrochloride as a yellow powder, quant. A sample of the product was further purified by reverse-phase preparative HPLC [C-18; 15-18% MeCN / 10 mM HCl]. RP-HPLC (1-90S) RT = 2.37 min. ¹H NMR (400 MHz, d₆-DMSO, selected signals): δ 10.40* (1H, br s), 9.33* (2H, s), 8.89* (2H, s), 8.83 (1H, d, $J = 2.0$ Hz), 8.18 (1H, d, $J = 0.8$ Hz), 7.93 (1H, d, $J = 2.0$ Hz), 7.86 (1H, d, $J = 8.4$ Hz), 7.73 (1H, dd, $J = 8.4, 2.0$ Hz), 7.71 (1H, d, $J = 2.0$ Hz), 7.67 (1H, dd, $J = 8.4, 2.4$ Hz), 7.16* (2H, s), 7.06 (1H, d, $J = 8.4$ Hz); m/z (LCMS-ESI): Q⁺ 468 (M+H), Q⁻ 466 (M-H).

[0266] EXAMPLE 10

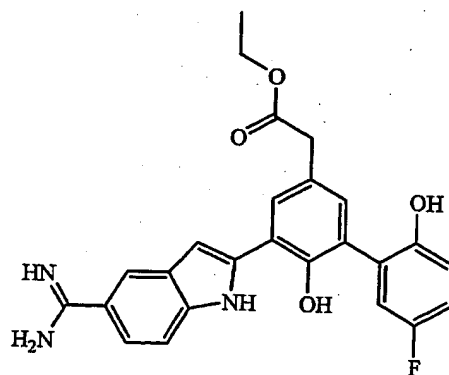
Synthesis of 5'-fluoro-5-[5-(N-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-6-(2-methoxy-ethoxymethoxy)-2'-methoxymethoxy-biphenyl-3-yl-acetic acid



[0267] Methyl [5-(5-cyano-1-methanesulfonyl-1*H*-indol-2-yl)-5'-fluoro-6-(2-methoxy-ethoxymethoxy)-2'-methoxymethoxy-biphenyl-3-yl]-acetic acid methyl ester (2.16 gm, 3.45 mmol), prepared by methods analogous to those set forth in the preceding examples, was dissolved in methanol (30 mL) and then sodium hydroxide (10% aq solution, 10 mL) was added to the solution. The mixture was heated at 50 °C for 2 hours, cooled to room temperature and concentrated by evaporation. The residue was dissolved in ethyl acetate and the solution was acidified with 5% citric acid to pH 4. An intermediate was isolated as a solid (1.78 gm) by normal extractive work-up and then dissolved in ethanol (25 mL). Hydroxylamine (50% aqueous, 6 mL) was added to the solution and the mixture was heated at 85 °C for 4 hours and then concentrated by rotary evaporation. The residue was dried under high vacuum overnight gave 5'-fluoro-5-[5-(N-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-6-(2-methoxy-ethoxymethoxy)-2'-methoxymethoxy-biphenyl-3-yl-acetic acid (2 gm) as a foam. LCMS calculated 567.2; found 568.0, M+1, 566.2, M-1.

[0268] EXAMPLE 11

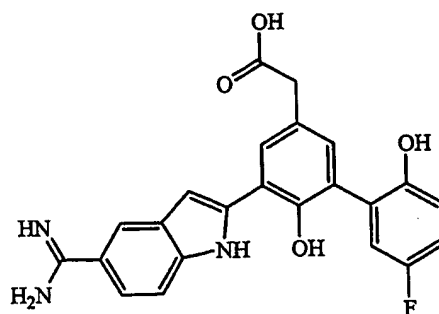
Synthesis of ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate



[0269] 5'-fluoro-5-[5-(N-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-6-(2-methoxyethoxymethoxy)-2'-methoxymethoxy-biphenyl-3-yl-acetic acid (0.66 gm, 1.16 mmol), prepared as in Example 10, was dissolved in acetic acid (15 mL) and then acetic anhydride (0.55 mL, 5.82 mmol) was added to the solution. The mixture stirred at room temperature for 1 hour and then concentrated by rotary evaporation followed by high vacuum. The residue was dissolved in ethanol (40 mL) and the compound was treated with Pd(OH)₂-C (40 mg, H₂ balloon) for 3 hours. The mixture was filtered and then concentrated under high vacuum. The residue (0.3 gm, 0.54 mmol) was dissolved in anhydrous ethanol (20 mL) and the solution was treated with hydrochloric acid (4 M in dioxane, 8 mL). The mixture was stirred at room temperature for 2 hours and concentrated. Purification of product from a small portion of the residue by reverse phase HPLC gave ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate as a light brown solid. ¹H NMR (DMSO-d₆) δ 11.62 (s, 1H), 9.09 (s, 2H), 8.62 (br s, 3H), 8.10 (d, 1H, *J* = 1.6 Hz), 7.59 (d, 1H, *J* = 1.9 Hz), 7.55 (d, 1H, *J* = 8.6 Hz), 7.44 (dd, 1H, *J* = 8.6, 1.9 Hz), 6.99 (m, 5H), 4.02 (q, 2H, *J* = 7.04 Hz), 3.61 (s, 2H), 1.17 (t, 3H, *J* = 7.04 Hz). LCMS calcd. 447.16, found 448.1, M+1, 446.3, M-1.

[0270] EXAMPLE 12

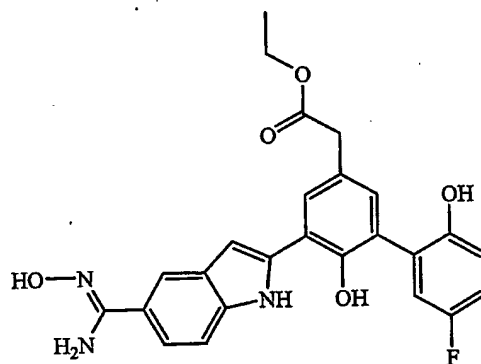
Synthesis of [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid



[0271] Ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate, prepared as in Example 11, was dissolved acetonitrile (20 mL) and the solution was treated with 1N hydrochloric acid (8 mL) at reflux for 1 hour. The mixture was concentrated and purification of product from the residue by reverse phase HPLC followed by lyophilization gave [5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid (0.1 gm, 42%) as a brown solid. ¹H NMR (DMSO-*d*₆) δ 11.72 (s, 1H), 10.10 (s, 1H), 9.09 (s, 2H), 8.72 (s, 2H), 8.61 (s, 1H), 8.05 (s, 1H), 7.60 (d, 1H, *J* = 1.9 Hz), 7.55 (d, 1H, *J* = 8.2 Hz), 7.46 (dd, 1H, *J* = 8.2, 1.6 Hz), 7.05 (d, 1H, *J* = 1.6 Hz), 7.01 (d, 1H, *J* = 1.9 Hz), 6.95 (m, 3H), 3.51 (s, 2H). LCMS calcd. 419.13, found 420.0, *M*+1, 418.3, *M*-1.

[0272] EXAMPLE 13

Synthesis of ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate



[0273] 5'-Fluoro-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-6-(2-methoxyethoxymethoxy)-2'-methoxymethoxy-biphenyl-3-yl-acetic acid (0.079 gm, 0.14 mmol),

prepared as in Example 10, was dissolved in anhydrous ethanol (10 mL) and the solution was treated with anhydrous hydrochloric acid (4 M in dioxane, 4 mL). The mixture was stirred for 3 hours at room temperature and then concentrated by evaporation. Purification of product from the residue by reverse phase HPLC gave ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate (0.028 gm, 43%), as a brown solid. ¹H NMR (DMSO-*d*₆) δ 11.75 (s, 1H), 10.89 (br s, 1H), 7.96 (s, 1H), 7.66 (d, 1H, *J* = 1.9 Hz), 7.61 (d, 1H, *J* = 8.2 Hz), 7.38 (dd, 1H, *J* = 8.2, 1.6 Hz), 7.05 (m, 5H), 4.11 (q, 2H, *J* = 7.0 Hz), 3.68 (s, 2H), 1.20 (t, 3H, *J* = 7.0 Hz). LCMS calcd. 463.15, found 464.0, *M*+1, 462.2, *M*-1.

Biological Examples

[0274] EXAMPLE 1

In Vitro Factor VIIa Inhibitor Assay

[0275] Mixtures of human Factor VIIa (typically supplied at 7 nM) and test compound (present at varying concentrations) in assay medium (comprising: NaCl, 150 mM (pH 7.4); CaCl₂, 5 mM; Tween-20, 0.05%; Dade Innovin tissue factor [Dade Behring, Newark, DE, USA]; EDTA, 1.5 mM; and dimethylsulfoxide, 10 %) were incubated for 30 minutes at room temperature. Next, reactions were initiated with the addition of substrate [500 μM of CH₃SO₂-D-Cha-But-Arg-pNA (from Centerchem, Norwalk, CT, USA)]. Hydrolysis of the chromogenic substrate was followed spectrophotometrically at 405 nm for five minutes. Initial velocity measurements calculated from the progress curves by a kinetic analysis program (Batch Ki; BioKin, Ltd., Pullman, WA) were used to determine apparent inhibition constants (apparent *K_i*'s).

[0276] Compounds of this invention tested by the above-described assay exhibited inhibition of Factor VIIa.

[0277] EXAMPLE 2

In Vitro Factor Xa Inhibitor Assay

[0278] Mixtures of human Factor Xa (typically supplied at 3 nM) (from Haematologic Technologies, Essex Junction, VT, USA) and test compound (varying concentrations) in assay medium (comprising: Tris, 50 mM (pH 7.4); NaCl, 150 mM; CaCl₂, 5 mM; Tween-20, 0.05%; EDTA, 1 mM; and dimethylsulfoxide, 10%) were incubated for 30 minutes at room temperature. Next, reactions were initiated with the addition of substrate [500 μM of CH₃CO₂-D-Cha-Gly-Arg-pNA (from Centerchem, Norwalk, CT, USA)]. Hydrolysis of the chromogenic substrate was followed spectrophotometrically at (405 nm) for five minutes.

Apparent inhibition constants (apparent K_i 's) were calculated from the enzyme progress curves using standard mathematical models.

[0279] Compounds of the invention tested by the above-described assay exhibited inhibition of Factor Xa.

[0280] EXAMPLE 3

Pharmacokinetic Assay

[0281] Rats with pre-implanted jugular vein catheters, which were filled with heparin/saline/PVP lock prior to shipment, were bought from Charles River. Three rats were selected for each study, weighed, and injected with test compound by tail vein injection. Any residual test compound was retained and stored at -70 °C for later analysis.

[0282] Blood samples (0.25 mL each) were collected from the indwelling catheters at specified times over 120 hours. The catheters were flushed with physiological saline immediately after each collection and filled with heparinized saline after each 8, 24 and 48 hour collection. In the event that a catheter failed, blood samples were collected via the retro-orbital sinus under isoflurane anesthesia at the appropriate time.

[0283] Blood samples were placed in 0.5 mL Microtainer® tubes (lithium heparin), shaken gently and stored on wet ice. The samples were centrifuged for 10 minutes at 2400 rpm in a refrigerated centrifuge. Plasma samples (0.1 mL) from each tube were transferred to 0.5 mL Unison polypropylene vials (Sun - 500210) and stored below -70 °C for later analysis by LC/MS-MS.

[0284] EXAMPLE 4

In vitro Clotting Assays..... aPTT and PT

[0285] Coagulation assays, activated partial thromboplastin time (aPTT) and prothrombin time (PT) were carried out based on the procedure described in Hougie, C. *Hematology* (Williams, W. J., Beutler, B., Erslev, A. J., and Lichtman, M. A., Eds.), pp. 1766-1770 (1990), McGraw-Hill, New York.

[0286] Briefly, the assays were performed using normal human citrated plasma and were performed at 37 °C on a coagulometer (Electra 800) in accordance with the manufacturer's instructions (Medical Laboratory Automation- Pleasantville, New York). The instrument was calibrated with plasma immediately prior to collecting clotting times for samples with inhibitors. The aPTT and PT doubling concentrations were calculated by fitting inhibitor dose response curves to a modified version of the Hill equation.

Pharmaceutical Composition Examples

[0287] The following are representative pharmaceutical formulations containing a compound of this invention.

Tablet Formulation

[0288] The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule Formulation

[0289] The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

[0290] The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 mL
colorings	0.5 mg
distilled water	q.s. to 100 mL

Injectable Formulation

[0291] The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	1.2 g
sodium acetate buffer solution,	0.4 M 2.0 mL
HCl (1 N) or NaOH (1 N)	q.s. to suitable pH

water (distilled, sterile) q.s.to 20 mL

[0292] All of the above ingredients, except water, are combined and heated to 60-70 °C. with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

[0293] A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15	balance

[0294] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

WE CLAIM:

1. A compound selected from the group consisting of:
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;
 - 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;
 - 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;
 - 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;
 - 5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-nitro-4'-methyl-6-hydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-6-hydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-indol-2-yl)-2',4'-difluoro-6-hydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-nitro-6-hydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methyaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;
 - 2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid;

3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-amino-6-hydroxy-biphenyl-3-yl]propionic acid;

3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid;

N-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;

ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;

[5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and

ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or
a pharmaceutically acceptable salt thereof.

2. A compound selected from the group consisting of:

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-yl]-2-methylpropionic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-2',4'-difluoro-5'-aminosulfonyl-6-hydroxy-biphen-3-ylcarboxylic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-methylaminosulfonyl-6-hydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(2-hydroxyethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-ureidomethyl-6-hydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonylmethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-hydroxymethyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminocarbonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-(thioureidomethyl)-6-hydroxy-biphenyl-3-yl]acetic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-aminosulfonyl-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid;

3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-3'-aminosulfonyl-6-hydroxy-biphenyl-3-yl]propionic acid;

3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-acetylaminomethyl-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid;

N-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;

ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;

[5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and

ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamimidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or

a pharmaceutically acceptable salt thereof.

3. A compound selected from the group consisting of:

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-yl]-2-methylpropionic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphen-3-ylcarboxylic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(3-methylureidomethyl)-2',6-dihydroxy-biphenyl-3-yl]acetic acid;

3-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-ureidomethyl-6,2'-dihydroxy-biphenyl-3-yl]propionic acid;

N-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;

ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;

[5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and

ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or

a pharmaceutically acceptable salt thereof.

4. A compound selected from the group consisting of:

N-[3'-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-5'-(1-carboxy-1-methyl-ethyl)-6,2'-dihydroxy-biphenyl-3-ylmethyl]-2*R*,3*R*-dihydroxy-succinamic acid;

2-[5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoylbiphenyl-3-yl]-2-methylpropionic acid;

5-(5-carbamimidoyl-1*H*-benzoimidazol-2-yl)-6,2'-dihydroxy-5'-sulfamoyl-biphenyl-3-carboxylic acid;

ethyl 5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl-acetate;

[5-(5-carbamimidoyl-1*H*-indol-2-yl)-5'-fluoro-6,2'-dihydroxy-biphenyl-3-yl]-acetic acid; and

ethyl 5'-fluoro-6,2'-dihydroxy-5-[5-(*N*-hydroxycarbamidoyl)-1*H*-indol-2-yl]-biphenyl-3-yl-acetate; or

a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1, 2, 3 or 4.

6. A method of treating a disease in an animal mediated by Factor VIIa which method comprises administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 2, 3 or 4 and a pharmaceutically acceptable carrier.
7. The method of Claim 6 wherein the disorder is a thromboembolic disorder or cancer.
8. The method of Claim 6 wherein the disorder is sepsis or deep vein thrombosis.
9. A method of treating a thromboembolic disorder, which method comprises administering to said animal a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1, 2, 3 or 4 in combination with another anticoagulant agent(s) independently selected from a group consisting of a thrombin inhibitor, a factor IXa, a factor Xa inhibitor, Aspirin®, and Plavix®.
10. A method for inhibiting the coagulation of a biological sample comprising the administration of a compound of Claim 1.
11. A method of treating a disease in an animal mediated by Factor VIIa which method comprises parenterally administering to said animal a pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 2, 3 or 4 and a pharmaceutically acceptable carrier.
12. The method of Claim 11 wherein the disorder is a thromboembolic disorder or cancer.
13. The method of Claim 11 wherein the disorder is sepsis or deep vein thrombosis.
14. The use of a compound of Claim 1, 2, 3 or 4 for the production of a pharmaceutical composition for the treatment of a disease in an animal mediated by Factor VIIa.

INTERNATIONAL SEARCH REPORT

Application No
PCT/US 03/41636

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/405 A61K31/4184 C07D209/42 C07D235/18 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/006011 A (RAI ROOPA ; AXYS PHARM INC (US); HENDRIX JOHN (US); HU HUIYONG (US); S) 23 January 2003 (2003-01-23) claims 1,29	1-14
P,X	WO 03/068756 A (RAI ROOPA ; YOUNG WENDY B (US); AXYS PHARM INC (US); KOLESNIKOV ALEKSA) 21 August 2003 (2003-08-21) claims 1,16 ----- -/--	1-14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

3 June 2004

Date of mailing of the international search report

11/06/2004

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Bérillon, L

INTERNATIONAL SEARCH REPORT

I Application No
PCT/US 03/41636

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YOUNG ET AL: "Optimization of a screening lead for factor VIIa/TF" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 11, no. 17, 3 September 2001 (2001-09-03), pages 2253-2256, XP002212336 ISSN: 0960-894X tables 1,2	1-14
X	WO 00/35886 A (SPENCER JEFFREY R ; RAI ROOPA (US); VERNER ERIK J (US); YOUNG WENDY B) 22 June 2000 (2000-06-22) claims 1,11; examples 176,178,179,182,186,445,446	1-14
A	WO 02/14307 A (LEAHY ELLEN M ; AXYS PHARM INC (US)) 21 February 2002 (2002-02-21) the whole document	1-14

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 03/41636

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 6-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Ir Application No
PCT/US 03/41636

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03006011	A	23-01-2003	CA 2452391 A1 EP 1408963 A1 WO 03006011 A1 WO 03006670 A2 US 2003114457 A1	23-01-2003 21-04-2004 23-01-2003 23-01-2003 19-06-2003
WO 03068756	A	21-08-2003	WO 03068756 A1	21-08-2003
WO 0035886	A	22-06-2000	AU 2711500 A BR 9916363 A CA 2355249 A1 CN 1344256 T CZ 20012006 A3 EE 200100323 A EP 1140859 A2 HU 0104987 A2 JP 2002532479 T NO 20012980 A NZ 512375 A PL 349192 A1 SK 7972001 A3 WO 0035886 A2	03-07-2000 11-12-2001 22-06-2000 10-04-2002 13-03-2002 15-08-2002 10-10-2001 29-07-2002 02-10-2002 01-08-2001 28-11-2003 01-07-2002 04-06-2002 22-06-2000
WO 0214307	A	21-02-2002	AU 8334001 A WO 0214307 A1 US 2002037912 A1	25-02-2002 21-02-2002 28-03-2002

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